

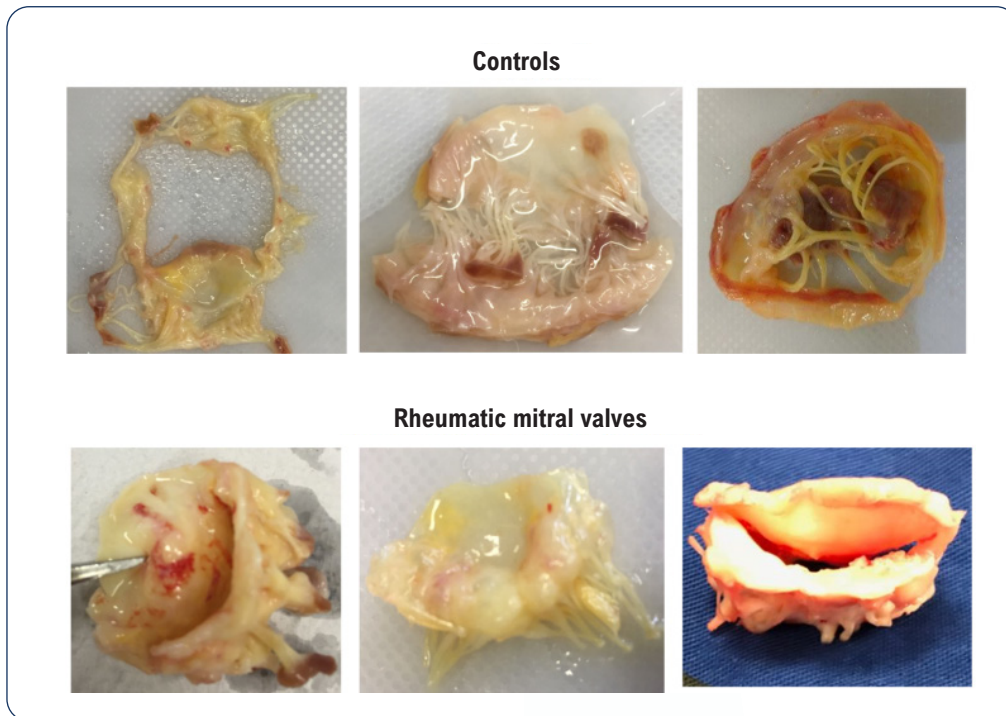


Figure 1, page 406

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The Method and the Mantra

Impact of COVID-19 on cardiovascular diseases

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Cardiovascular Risk in the Brazilian Population

Cardiac Rehabilitation and Mean Platelet Volume

Infliximab therapy in resistant hypertension

Validation of ECG Algorithm for VT

Gensini, thrombus burden and SYNTAX in no-reflow

Contents

Editorial

The Method and the Mantra

Andre d'Avila and Marcos F. Vidal Melo

.....page 367

Original Article

Reduction in Hospitalization and Increase in Mortality Due to Cardiovascular Diseases during the COVID-19 Pandemic in Brazil

Paulo Garcia Normando, José de Arimatéia Araujo-Filho, Gabriela de Alcântara Fonseca, Rodrigo Elton Ferreira Rodrigues, Victor Agripino Oliveira, Ludhmila Abrahão Hajjar, André Luiz Cerqueira Almeida, Edimar Alcides Bocchi, Vera Maria Cury Salemi, Marcelo Melo

.....page 371

Short Editorial

Avoidable Cardiovascular Events: A Serious Side Effect of the COVID-19 Pandemic

Fernando H. Y. Cesena

.....page 381

Original Article

Prognostic Value of Lung Ultrasound for Clinical Outcomes in Heart Failure Patients: A Systematic Review and Meta-Analysis

Yushu Wang, Di Shi, Fuqiang Liu, Ping Xu, Min Ma

.....page 383

Short Editorial

Is There a Role for Lung Ultrasonography in the Prognosis of Heart Failure Patients?

Mônica Samuel Avila e Deborah De Sá Pereira Belfort

.....page 393

Original Article

Mortal Interaction Between Hemophagocytic Syndrome and Newly Developed Heart Fail

Devrim Bozkurt, Sukriye Miray Kilincer Bozgul, Omer Emgin, Osman Butun, Timur Kose, Evrim Simsek, Mine Hekimgil, Salih Kilic

.....page 395

Short Editorial

Hyperinflammatory Syndrome as a Cardiac Injury Mechanism

Silvia Moreira Ayub-Ferreira e Maria Tereza Sampaio de Sousa Lira

.....page 402

Original Article

Histopathological Characterization of Mitral Valvular Lesions from Patients with Rheumatic Heart Disease

Nayana F. A. Gomes, Marcelo A. Pascoal-Xavier, Livia S. A. Passos, Thiago Mendonça Nunes Paula, João Marcelo de Souza Aguiar, Felipe Vieira Guarçoni, Maria Cecília Landim Nassif, Claudio Leo Gelape, Renato Braulio, Paulo Henrique N. Costa, Luiz Guilherme Passaglia, Raquel Braga Martins, Walderez O. Dutra, Maria Carmo P. Nunes

.....page 404

Short Editorial

Histopathological Characterization of Mitral Valvular Lesions in Patients With Rheumatic Heart Disease: Is Inflammation Also to Blame for Chronic Valvular Heart Disease Progression?

Vitor Emer Egypto Rosa

.....page 413

Original Article

Inhibiting Glucose Metabolism By miR-34a and miR-125b Protects Against Hyperglycemia-Induced Cardiomyocyte Cell Death

Chao-rui Xu and Qiu-ju Fang

.....page 415

Original Article

Cardiovascular Risk Estimates in Ten Years in the Brazilian Population, a Population-Based Study

Deborah Carvalho Malta, Pedro Cisalpino Pinheiro, Renato Azeredo Teixeira, Isis Eloah Machado, Filipe Malta dos Santos, Antônio Luiz Pinho Ribeiro

.....page 423

Short Editorial

“Know the Enemy and Know Yourself”. Cardiovascular Risk in the National Health Survey

Itamar S. Santos

.....page 432

Original Article

Exercise-Based Cardiac Rehabilitation Has a Strong Relationship with Mean Platelet Volume Reduction

İsmet Durmuş, Ezgi Kalaycıoğlu, Mustafa Çetin, Hanife Baykal Şahin, Tuncay Kırış

.....page 434

Short Editorial

Reduction in Platelet Activation: A Potential Mechanistic Link between Regular Exercise and Its Benefits for Coronary Artery Disease

Christina Grüne de Souza e Silva

.....page 441

Original Article

Effects of Anti-TNF alpha Therapy on Blood Pressure in Resistant Hypertensive Subjects: A Randomized, Double-Blind, Placebo-Controlled Pilot Study

Ana Paula de Faria, Alessandra M. V. Ritter, Arthur Santa-Catharina, Débora P. Souza, Estephania P. Naseri, Manoel B. Bertolo, Mariana Rodrigues Pioli, Caio C. Carvalho, Rodrigo Modolo, Heitor Moreno

.....page 443

Short Editorial

New Perspectives in the Treatment of Hypertension

Heno F. Lopes

.....page 452

Original Article

Validation of a Simple Electrocardiographic Algorithm for Detection of Ventricular Tachycardia

Francisco Santos Neto, Cristiano F. Pisani, Francisco Carlos da Costa Darrieux, Celia M. F. Cirino, Denise Tessariol Hachul, Astrid M. Santos, Andrés Ricardo Pérez-Riera, Raimundo Barbosa-Barros, Mauricio Scanavacca

.....page 454

Short Editorial

Simplified Algorithm for Differential Diagnosis of Tachycardias with Wide QRS. Is this the Best Way to Train Young Doctors?

Enrique Indalécio Pachón Mateo

.....page 464

Original Article

Gensini Score and Thrombus Burden Add Predictive Value to the SYNTAX Score in Detecting No-Reflow after Myocardial Infarction

Luís Carlos V. Matos, Luiz Sergio Carvalho, Rodrigo Modolo, Simone Santos, José Carlos Quinaglia e Silva, Osório Luis Rangel de Almeida, Andrei C. Sposito

.....page 466

Short Editorial

Angiographic Scores in Prediction of No-Reflow, Myocardial Injury May not end with Reperfusion

Adriano Ossuna Tamazato, Thais Chang Valente Tamazato, Cristiano Guedes Bezerra

.....page 473

Original Article

Arterial Stiffness Changes in Severe Aortic Stenosis Patients Submitted to Valve Replacement Surgery

Renata Raimundo, Francisca Saraiva, Raquel Moreira, Soraia Moreira, Ana Filipa Ferreira, Rui J. Cerqueira, Mario Jorge Amorim, Paulo Pinho, António Sousa Barros, André P. Lourenço, Adelino Leite-Moreira

.....page 475

Short Editorial

Arterial Stiffness in Aortic Stenosis

Henrique Murad

.....page 483

Original Article

Kawasaki Disease: Predictors of Resistance to Intravenous Immunoglobulin and Cardiac Complications

Diogo Faim, Cláudio Henriques, Ana Brett, Andreia Francisco, Fernanda Rodrigues, António Pires

.....page 485

Short Editorial

Kawasaki Disease: Predictors of Intravenous Immunoglobulin Resistance and Cardiac Complications: New Perspectives?

Isabel Cristina Britto Guimarães

.....page 492

Review Article

GDF-15 as a Biomarker in Cardiovascular Disease

Bruna Miers May, Mauricio Pimentel, Leandro Ioschpe Zimerman, Luis Eduardo Rohde2

.....page 132

Research Letter

What are the Optimal Reference Values for Home Blood Pressure Monitoring?

Audes D. M. Feitosa, Marco A. Mota-Gomes, Fernando Nobre, Decio Mion Jr., Annelise M.G. Paiva, Fábio Argenta, Weimar K.S. Barroso, Roberto D. Miranda, Eduardo C. D. Barbosa, Andréa A. Brandão, Thiago S.V. Jardim, Paulo C.B.V. Jardim, Wilson Nadruz

.....page 501

Research Letter

Early vs. Late Neutrophil-To-Lymphocyte Ratio for the Prediction of Adverse Outcomes in Patients with STEMI Undergoing Primary PCI

Guilherme Pinheiro Machado, Gustavo Neves de Araujo, Daniele Maltauro, Julia Custodio, Victoria Milan, Marco Wainstein

.....page 504

Research Letter

Three-Dimensional-Printed Heart Prototype for Application in Pediatric Cardiology: An Initial Experiment

Maíra Levorato Basso, Alessandra Möbius Gebran, Julia Dullius Oliveira, Katrin Möbius Gebran, Letícia Carlota Bonatto, Maria Cecília Knoll Farah
.....page 507

Letter to the Editor

Serum Levels of BDNF in Cardiovascular Protection and in Response to Exercise

Carla Paixão Miranda, Fernando Antônio Botoni, Manoel Otávio da Costa Rocha
.....page 510

Image

Acute Myocardial Infarction with Coronary Thrombosis in a Covid-19 Patient without Risk Factors for Cardiovascular Disease

Tainá Viana, Mariana Lins Baptista Guedes Bezerra, Rodrigo Morel Vieira de Melo, Cristiano Guedes Bezerra, Vítor Mamédio, Gabriela Pio Dourado, Clara Salles Figueiredo, Luiz Carlos Santana Passos
.....page 511

Guidelines

Brazilian Guidelines of Hypertension – 2020

Weimar Kunz Sebba Barroso, Cibele Isaac Saad Rodrigues, Luiz Aparecido Bortolotto, Marco Antônio Mota-Gomes, Andréa Araujo Brandão, Audes Diógenes de Magalhães Feitosa, Carlos Alberto Machado, Carlos Eduardo Poli-de-Figueiredo, Celso Amodéo, Décio Mion Júnior, Eduardo Costa Duarte Barbosa, Fernando Nobre, Isabel Cristina Britto Guimarães, José Fernando Vilela-Martin, Juan Carlos Yugar-Toledo, Maria Eliane Campos Magalhães, Mário Fritsch Toros Neves, Paulo César Brandão Veiga Jardim, Roberto Dischinger Miranda, Rui Manuel dos Santos Póvoa, Sandra C. Fuchs, Alexandre Alessi, Alexandre Jorge Gomes de Lucena, Alvaro Avezum, Ana Luiza Lima Sousa, Andrea Pio-Abreu, Andrei Carvalho Sposito, Angela Maria Geraldo Pierin, Annelise Machado Gomes de Paiva, Antonio Carlos de Souza Spinelli, Armando da Rocha Nogueira, Nelson Dinamarco, Bruna Eibel, Cláudia Lúcia de Moraes Forjaz, Claudia Regina de Oliveira Zanini, Cristiane Bueno de Souza, Dilma do Socorro Moraes de Souza, Eduardo Augusto Fernandes Nilson, Elisa Franco de Assis Costa, Elizabete Viana de Freitas, Elizabeth da Rosa Duarte, Elizabeth Silaid Muxfeldt, Emilton Lima Júnior, Erika Maria Gonçalves Campana, Evandro José Cesarino, Fabiana Marques, Fábio Argenta, Fernanda Marciano Consolim-Colombo, Fernanda Spadotto Baptista, Fernando Antonio de Almeida, Flávio Antonio de Oliveira Borelli, Flávio Danni Fuchs, Frida Liane Plavnik, Gil Fernando Salles, Gilson Soares Feitosa, Giovannio Vieira da Silva, Grazia Maria Guerra, Heitor Moreno Júnior, Helius Carlos Finimundi, Isabela de Carlos Back, João Bosco de Oliveira Filho, João Roberto Gemelli, José Geraldo Mill, José Marcio Ribeiro, Leda A. Daud Lotaif, Lilian Soares da Costa, Lucélia Batista Neves Cunha Magalhães, Luciano Ferreira Drager, Luis Cuadrado Martin, Luiz César Nazário Scala, Madson Q. Almeida, Marcia Maria Godoy Gowdak, Marcia Regina Simas Torres Klein, Marcus Vinícius Bolívar Malachias, Maria Cristina Caetano Kuschner, Maria Eliete Pinheiro, Mario Henrique Elesbão de Borba, Osni Moreira Filho, Oswaldo Passarelli Júnior, Otavio Rizzi Coelho, Priscila Valverde de Oliveira Vitorino, Renault Mattos Ribeiro Junior, Roberto Esporcatte, Roberto Franco, Rodrigo Pedrosa, Rogerio Andrade Mulinari, Rogério Baumgratz de Paula, Rogério Toshiro Passos Okawa, Ronaldo Fernandes Rosa, Sandra Lia do Amaral, Sebastião R. Ferreira-Filho, Sergio Emanuel Kaiser, Thiago de Souza Veiga Jardim, Vanildo Guimarães, Vera H. Koch, Wille Oigman, Wilson Nadruz
.....page 516

Statement

Position Statement on Indications and the Safe Reintroduction of Cardiovascular Imaging Methods in the COVID-19 Scenario – 2021

Adenalva Lima de Souza Beck, Silvio Henrique Barberato, André Luiz Cerqueira de Almeida, Claudia R. Pinheiro de Castro Grau, Marly Maria Uellendahl Lopes, Ronaldo de Souza Leão Lima, Rodrigo Júlio Cerci, Ana Cristina Lopes Albricker, Fanilda Souto Barros, Alessandra Joslin Oliveira, Edgar Bezerra de Lira Filho, Marcelo Haertel Miglioranza, Marcelo Luiz Campos Vieira, José Luiz Barros Pena, Tânia Mara Varejão Strabelli, David Costa de Souza Le Bihan, Jeane Mike Tsutsui, Carlos Eduardo Rochitte

.....page 659



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The Method and the Mantra

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Introduction

At the time of the residency in Cardiology, a patient chose to become a vegetarian after having a metallic heart valve implanted. Until that day, he proudly announced that he only ate meat, rice and beans! He had spent years without eating a lettuce leaf, but as a friend suggested that this type of diet increased the risk of calcification of the other heart valves, he chose to change it, even before checking the veracity of the information.

He had been warned that a diet rich in vegetables could make it difficult to handle anticoagulation, but he had no doubts: he had found the motivation to live a healthier life after the surgery. He proudly eliminated meats and chose vegetables, instead. He felt much better and he no longer had shortness of breath. Convinced of the benefits of his new lifestyle, he died 6 months after surgery due to intracranial hemorrhage, as he had to take more anticoagulants to compensate for the diet... Our patient got the mantra right, but not the method. He opted for a supposedly healthier life that was wrongly put into practice, at the wrong time and was unable to enjoy his discipline or the new lifestyle.

A mantra represents a deep conviction, summed up in a phrase, word or attitude that is repeated in order to achieve a state of communion with oneself and the environment where we live. The method is an organized process, technique or way of doing something, according to a logical plan, aiming to achieve a previously defined objective. The method must be clear enough to be reproduced. The mantra is less tangible, more conceptual. Method and mantra can be responsible for the success or failure of innumerable initiatives. More often than the mantra, the method is often questioned and it is generally assumed that the method needs to be revised, when an objective cannot be achieved. Less frequently, the mantra is discussed because it is based on axioms. But the mantra and the method are inseparable.

Disagreements in the Pandemic

In a moment of complete irrationality regarding the COVID-19 pandemic, which, in addition to the sad number of fatalities, is characterized by a disparity of opinions, conduct and a search for a redeeming solution,¹ it is worth asking about what went wrong: mantra or method? Or were both, method and mantra, wrong?

Keywords

COVID-19; Pandemics; Schools Medical; Health Sciences; Technology and Innovation Management; Medical Education; Doctor's Degree.

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Even with effects that go far beyond health issues, the pandemic is essentially a medical problem. However, the inability and unpreparedness of health systems to propose effective solutions has been evident throughout the world. It is as if all the training, knowledge and experience with historically similar situations, had been forgotten or was insufficient and inadequate to deal with the current situation. I cannot prove it, but if a coordinated action plan had been implemented, better results would have been obtained, fewer lives would have been lost and there would have been fewer sequelae. If not for the almost instinctive dedication of selfless health professionals, who are the real heroes in this whole mess, the disaster could have been even greater.

During the 2009 financial crisis, a cohesive plan and rapid and coordinated action by the central banks minimized the crisis. It was a financial problem that was solved by the group of financial experts. What is going wrong in the pandemic, then? Why are health systems and their leaders unable to propose an orderly action? Mantra and method seem hopelessly disconnected here.

Recurring Mantras, Proposed Methods and Their Consequences:

We have been long listening to three recurring mantras related to medical practice and Medicine in Brazil. For each mantra, a method has been proposed. The first one suggests that the country needs doctors and, therefore, more and more doctors are essential. Problem solved: several medical schools were opened throughout the country.

The second mantra focuses on the doctors' need for academic improvement: more science to better serve! In response to that, the 'Final Term Paper' was created in 1983 and postgraduate school grew.

Finally, the most recent of the mantras, recommends complementing medical training with business improvement courses to facilitate the communication between doctors and administrators. Doctors and managers together, speaking the same language – marketing, finance, human resources, accounting – would inevitably improve care. Therefore, never have so many doctors attended a Master in Business Administration (MBA) course as in recent years.

In principle, the three components could have converged to the greater good: more doctors with better academic training, tuned in and working side by side with managers! Mantra and method in harmony. However, the scenario we see is quite different from the one we imagined. It seems like the opposite has happened: many more doctors with inadequate training, without any aptitude for the scientific method and unable to understand the stringency of research, working not in partnership, but under the control of health managers. Mantra and method in dissonance.

We will try to assess how these variables may have influenced, either separately or together, resulting in the complete disarticulation that continues to occur during the pandemic. Of course, these are peculiarities of the Brazilian reality and do not explain the meager capacity of health systems to react in many countries (not all). Perhaps, we are even using the pandemic as a pretext for this reflection and we might be accused of opportunism when trying to debate issues not necessarily connected to it; however, let us get to the facts.

Inadequate number of physicians in Brazil

Brazil has approximately 450,000 doctors almost symmetrically divided between men and women: 2.2 doctors per 1,000 inhabitants.² It seems a pretty reasonable number. Therefore, in a country with around 200 million inhabitants, we have 350 medical schools, 105 public and 245 private ones. The United States has 300 million people and 131 medical schools; China has 1.3 billion people and 150 medical schools. In Brazil, we have trained 30,000 new doctors every year for at least 5 years. There are 15 doctors per 100,000 inhabitants per year, a number far from that found in countries such as Denmark, which in 2015 had 23 medical graduates per 100,000 inhabitants.

Apparently, the numbers do not talk to each other, given the huge discrepancy. This is because there seems to be no magical number. It all depends on how health systems are structured in each country. It is obvious, however, that there is a number below which the quality of care is compromised, but another one above which the quality does not improve. And that number varies between countries, health regions and systems. We do not intend to determine herein what the appropriate number for Brazil is, but it is supposed to be 2.5 doctors per 1,000 inhabitants. It is thought that this number refers to well-trained doctors but this information is neither known nor discussed. However, as in all professions, the work of 10 poorly-qualified professionals can be done by a single well-qualified one. Therefore, it is of no use if the doctor/inhabitant ratio is adequate, if the quality of the professional is not.

Right or wrong, given the tremendous competition for vacancies, the system of access to medical courses continues to select a group of talented young people who end up being underutilized for lack of opportunity inside the medical schools. In many of them, for instance, there is no proximity between medical schools and hospitals to provide the student with the necessary training. In others, there are not enough medical residency programs to accommodate all medical graduates. And the residency is a vital part of the medical training. The cause of this poor performance, therefore, does not seem to be the students' fault, but the poor quality of training in many medical schools, which are not ready for the complex task of training a doctor in 6 years.

Moreover, Brazil will always be in need of physicians as long as it is the exclusive obligation of a physician to change a prescription, fill out an exam request, make a prenatal assessment, perform an exercise test or an abdominal ultrasound. We will never reach the ideal number of professionals as long as the "medical act" – created by doctors themselves – continues to justify the unplanned opening of medical schools across the country. The mantra and the method, therefore, have to change.

Forget the obsession with numbers – assuming that everything can be solved if there are enough people – and focus on improving quality so that the size of the workforce can be resized.

Research Incentive

Amid this hubbub, a subterfuge was created, which is incomprehensible from my viewpoint, called 'Final Term Paper' (FTP). The FTP is not part of the National Curricular Guidelines for the Medical Course but has been used in private and some public colleges, as a local institutional rule. In theory, it is a mandatory academic work and an instrument for the final evaluation of a higher education course, prepared in the form of a dissertation, aiming at the student's initiation and involvement with scientific research. What would the premise of this requirement have been if it did not suggest that conducting research or scientific work improves the medical doctor's qualification?

I do not know about other disciplines, but there is nothing more wrong than applying this concept to Medicine. There are countless examples of very talented doctors who have no aptitude for research, as well as excellent researchers who do not feel comfortable interacting with patients. Occasionally, the two interests can converge on the same professional, without making it necessarily better on either side. Clinical excellence does not depend on research excellence. Doctors can and must learn to interpret scientific articles without having to carry out such research. This would indeed be vital, to avoid that in crises such as the current one, unscientific postures be adopted. Who knows, we would not have to go through the embarrassing situation of disputing the importance and role of randomized clinical trials compared to observational studies. In this sense, the FTP is of little help: those who like research do not need it to continue researching. Those who do not like research, feel used and their interest, which was already scarce, disappears. The FTP should be optional, and the best papers should be duly recognized, promoted and awarded to inspire other students.

The FTP requirement contrasts head-on with the relatively easy acceptance to participate in a doctorate in Medicine. In some programs, the doctoral thesis will be the first and only work submitted by the author. Very often, the work and the research grant associated to it, is used exclusively to maintain the doctor's relationship with the hospital and not to achieve the primary purpose of getting a PhD: the advancement of knowledge in a specific area, through the production of unprecedented and high-level knowledge, made by someone who seeks scientific and / or academic growth under the guidance of people and groups who have deep knowledge in those areas of study. The doctorate should represent the apex of the career and not an end in itself. Therefore, it cannot be used as an instrument to encourage research.

Moreover, few Brazilian universities use the system for compilation of the author's work inside a given line of research. As an example of a different approach to the doctorate, last year, one of the authors participated in two doctorate Board of Examiners of Australian doctors. The work was sent by e-mail: a compendium of more than 500 pages, bringing together several contributions by the author (unprecedented works published in scientific journals with independent reviewers) on the addressed topic and a final summary connecting all these observations

into a relevant conclusion. Therefore, the evaluator does not interact with the student, maintaining the impersonality and concentrating on the value of the work, which are proper under this circumstance. The evaluator's considerations are sent to the university, which decides whether the student deserves the Ph.D. title.

This experience contrasts with some of the national ones where, sometimes, friends and family participate in the presentation of the doctoral work, without that work and its author going through the appropriate scientific screening. In theory, this would be the role of the qualification class. Commonly, however, the team selected for the examination does not have the impact of the members of the final board. Ideally, it would be exactly the opposite: the board that comprises the examination class, including the greatest authorities on the subject and young researchers, aiming to accolade them, should evaluate the final thesis presentation. We insist on doing the opposite, because there is an expectation of validating the process, before it has actually been validated. Perhaps that is why there is a huge interest in obtaining a Ph.D. degree in Medicine in Brazil. In other countries, physicians of great academic prominence do not have a doctorate and are not interested in having the title. Much more important than the degree itself is the contribution to knowledge.

The quality of research, however, whether or not added to postgraduate programs, is essential to assess hospitals and educational institutions. Invariably, the institution's category is associated with the performance of research: the more research, the better the institution. For this reason, large hospitals encourage the interaction between doctors and researchers. In Brazil, the equation becomes more complicated, since the vast majority of the national medical scientific production is carried out in public colleges or in hospitals linked to these colleges, which, as a rule, have fewer resources and are unable to offer the same level of care to patients as private hospitals do, where there is little academic production. Therefore, there is no incentive for research in private hospitals and colleges. Evidently, there are exceptions, but this is the rule. One hopes these exceptions will serve as inspiration for the strategic planning of others. Appropriate mantra, but wrong method: there is a complete inversion of values in relation to the stimulation of research in Brazil.

MBA for Medical Doctors

To further complicate this entire situation, another disparity seems evident to us. Many physicians, throughout their careers,

are legitimately interested in learning about management. Several opportunities for improvement are available in this area. Many professionals are invited to take such courses, sometimes offered by the hospital itself, where they concentrate their activities. All of this seems valid, but perhaps a more reasonable and balanced approach would be possible: for each physician taking an MBA, a manager would be enrolled in a course of the same duration to learn how to understand the foundation of medical thinking.

For the time being, the mantra insists that we doctors need to better understand the intricate business relationship involved in providing the service. But we are physicians, not service providers. We do not have customers; we have patients. The perspectives of doctors and managers are completely different ones, because the decision regarding the individual, their health, and their life, is always more complex. Many managers do not know this point of view: the group is impersonal, the individual is not. The manager's failure or success impacts his bonus. The doctor's decision has other consequences. Although it seems reasonable to suggest that physicians should learn the managers' language to improve the quality and efficiency of the service provided by them, the inverse hypothesis cannot be ignored. Unfortunately, most medical managers invariably assume the role of managers' representative to the group of doctors; never the other way around. Instead of innovating, they become mere caretakers of pre-existing processes and the collaboration gets stalled.

What should be done?

We must redesign the mantra and the method to reconcile the interests between doctors, patients, population and managers. The general concept is a simple one: better medical schools, encouraging each student's natural talent, whether or not related to research, creating a professional identity that allows us to interact on an equal basis with other actors involved in the provision of medical service, centered on institutions that value research to guide their strategic planning and, for that reason, become a reference. Perhaps by doing this, we will have better luck in the next pandemic.

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Reduction in Hospitalization and Increase in Mortality Due to Cardiovascular Diseases during the COVID-19 Pandemic in Brazil

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Abstract

Background: In the COVID-19 pandemic, the increase in the incidence of cardiovascular diseases (CVD) and mortality from them has been recognized worldwide. In Brazil, the impact of COVID-19 on CVD must be evaluated.

Objectives: To assess the impact of the current pandemic on the numbers of hospital admissions (HA), in-hospital deaths (ID), and in-hospital fatality (IF) from CVD by use of national epidemiological data from the Brazilian Unified Public Health System.

Methods: Time-series observational study using comparative analysis of the HA, ID, and IF due to CVD recorded from January to May 2020, having as reference the values registered in the same period from 2016 to 2019 and the values projected by linear regression methods for 2020. The statistical significance level applied was 0.05.

Results: Compared to the same period in 2019, there was a 15% decrease in the HA rate and a 9% decrease in the total ID due to CVD between March and May 2020, followed by a 9% increase in the IF rate due to CVD, especially among patients aged 20-59 years. The HA and IF rates registered in 2020 differed significantly from the projected trend for 2020 ($p = 0.0005$ and 0.0318 , respectively).

Conclusions: During the first months of the pandemic, there were a decline in HA and an increase in IF due to CVD in Brazil. These data might have resulted from the inadequate planning of the CVD management during the pandemic. Thus, immediate actions are required to change this scenario. (Arq Bras Cardiol. 2021; 116(3):371-380)

Keywords: COVID-19; Betacoronavirus; Pandemics; Cardiovascular Diseases/complications; Epidemiology; Hospitalization; Mortality; Comorbidities; Unified Health System.

Introduction

The outbreak of the coronavirus disease 2019 (COVID-19) was declared a pandemic by the World Health Organization on March 11, 2020. In July 2020, Brazil ranked second in the number of cases and deaths from COVID-19. By July 24, 2020, Brazil had recorded 2 276 860 confirmed cases of COVID-19 and 84 551 deaths from the disease.¹⁻³

Considering that COVID-19 is spread primarily via droplets expelled during talking, coughing, and sneezing, or via contaminated surfaces,⁴ restrictions to people traffic and contact have been proposed by government and public health authorities in most western countries. In Brazil, the logistic

challenges to meet the patients' demands have included not only the increase in the number of beds in intensive care units and wards, but also the suspension of elective healthcare provision and of elective complementary tests and procedures, in addition to targeting public resources at the COVID-19 management.⁵⁻⁷

Population studies in other countries have reported a relative reduction in hospital admissions for cardiovascular diseases (CVD) during the COVID-19 pandemic,^{8,9} in association with an increase in the fatality rates related to that group of diseases,^{10,11} a reason for great concern in the international medical and scientific community.

Thus, we tested the hypothesis that, during the COVID-19 pandemic, there was a reduction in cardiovascular care provision and in the number of cardiovascular interventions performed, which might have led to higher in-hospital mortality from CVD in the general population. Using public databases from the Brazilian Unified Public Health System (SUS), this study aimed at assessing the impact of the pandemic on the number of hospital admissions and on in-hospital fatality due to CVD in Brazil from January to May 2020, as compared to those in the same months of the previous 4 years.

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In addition, pre-hospital clinical elements, such as elective procedures, were assessed.

Methods

This is a time-series observational study to assess the hospital admissions, in-hospital deaths, and in-hospital fatality rates (percentage of deaths among the admissions) related to CVD at SUS own units or at healthcare units with which SUS maintains an agreement, from January to May of the years 2016 to 2020. In addition, CVD-related in-hospital and outpatient procedures performed at those units during the same periods were assessed. The first two variables were classified according to age group as follows: child/adolescent (0-19 years), adult (20-59 years), and elderly (60 years and older). Data were collected on July 9, 2020, from the Brazilian Hospital Information System and Brazilian Outpatient Information System of the SUS (SIH and SIA/SUS, respectively), available at the DATASUS platform. Those systems are public and anonymous, in accordance with the first article of the Resolution 510/2016 of the Brazilian Committee on Ethics and Research. It is worth noting that updates on past admissions can occur in the platform at any time, thus, it is not guaranteed that all data are consolidated, regardless of the year.

For the analysis of the procedures, we used the codes of the SUS System for the Management of the Table of Procedures, Medications, Orthoses, Prostheses and Materials (SIGTAP). For each procedure selected, the in-hospital and outpatient productions were added, considering all correlated procedure codes. The procedures were as follows:

Diagnostic procedures: cardiac catheterization, echocardiography (stress, transesophageal, and transthoracic), electrocardiography, cardiac pacemaker implantation, 24-hour Holter monitoring, ambulatory blood pressure monitoring (ABPM), exercise test.

Surgical procedures: cardiovascular, endovascular, and vascular surgeries.

To assess the number of admissions, in-hospital deaths, and in-hospital fatality, we selected, for each age group, the records of the secondary diagnoses related to the corresponding cardiovascular pathologies in the List of Morbidity of the 10th Revision of the International Statistical Classification of Diseases and Related Health Problems (CID-10). The following disease categories were considered: stroke, hypertensive diseases (essential arterial hypertension and other hypertensive diseases), rheumatic diseases (acute rheumatic fever and chronic rheumatic heart disease), acute myocardial infarction (AMI), heart failure, congenital malformations of the circulatory system, and conduction disorders and arrhythmias.

Statistical Analysis

Considering that the procedures and surgeries are discriminated in the system regarding only their nature (outpatient or in-hospital), a descriptive analysis of how such procedures were distributed in those categories was performed. Regarding data from admission and in-hospital deaths, the variables sex, age group, skin color/race, and type of healthcare (urgency or emergency) were considered.

Aiming at understanding the possible impact of the pandemic on the dynamics of the procedures, admissions, and in-hospital

deaths related to CVD, the numbers regarding the months of March, April, and May – the most affected months of 2020 by the pandemic in Brazil – were compared for the years 2016 to 2020. The values recorded from 2019 and 2020 and their corresponding percent variation were compared. It is worth noting that a variation in the number of admissions and in-hospital deaths from one year to the other or a change in the mean of the previous years as compared to 2020 is not necessarily caused by the pandemic. We considered this hypothetical variation a possible consequence of an already established trend in the previous years. Finally, the value expected for the year 2020 was estimated by use of linear regression. Such analysis allows assuming whether the number of procedures, surgeries, admissions, and in-hospital deaths or the in-hospital fatality rate observed in the previous years showed a trend towards increase or decrease. Thus, that analysis captured both the trend of the years and the statistical variations occurring in the previous years.

Although normality tests were not performed, the normal distribution of data over time was assumed, considering the central limit theorem, because the data of each year are a totalization of several random variables. Homocedasticity could not be completely verified, because DATASUS does not provide completely individualized data.

Statistical analyses were performed for both the number of surgeries and procedures, and for each individual procedure/surgery as well. Similarly, those analyses were performed for admissions, in-hospital deaths, and in-hospital fatality, considering each morbidity studied individually as well as the sum of all of them, which is an analysis of the cardiovascular causes in general.

Because linear regression has a gaussian error, Student *t* test was performed for the mean of a sample to compare the values projected with those recorded in 2020, and the null hypothesis was rejected with $p < 0.05$ (95% confidence interval). The Microsoft® Excel® and Scilab® 6.1.0 software were used to perform the statistical analyses described and to build the tables and graphs.

Results

Descriptive Analysis

Based on the data collected regarding the months from January to May of the years 2016 to 2020, we identified 35 744 058 procedures, 1 336 472 hospital admissions, and 142 157 in-hospital deaths, and the last two were divided according to region, sex, age group, race/skin color, and healthcare type as shown in Table 1. Complete data illustrating the variation in the numbers initiating in March 2020 are shown in the figures of the supplementary material.

Graph Analysis

1A shows the data regarding the diagnostic and surgical procedures performed from March to May of 2016 to 2020. In addition, the estimates for 2020 (dotted lines), calculated by using data from 2016 to 2019, are also shown. A trend towards an increase in the number of diagnostic and surgical procedures (dotted lines) for the year 2020 is observed. However, the real data show a significant decrease when compared to data from the previous year.

Original Article

Table 1 – Descriptive analysis of the number of procedures, surgeries, admissions, and in-hospital deaths from January to May of the years 2016 to 2020

		IN-HOSPITAL		OUTPATIENT	
		Quantity	Percentage	Quantity	Percentage
Procedures					
	Adult cardiac catheterization	209 926	3.66%	252 162	0.87%
	Echocardiography	989 776	17.24%	2 751 796	9.53%
	Electrocardiography	4 461 799	77.71%	21 587 674	74.75%
	Pacemaker implantation	48 666	0.85%	-	-
	ABPM	-	-	2 763 748	9.57%
	Holter monitoring	26 119	0.45%	513 471	1.78%
	Exercise test	5 630	0.10%	1 010 144	3.50%
	Total	5 741 916	100.00%	28 878 995	100.00%
Surgeries					
	Cardiovascular	193 787	36.45%	-	-
	Endovascular	48 024	9.03%	-	-
	Vascular	289 815	54.51%	591 521	100.00%
	Total	531 626	100.00%	591 521	100.00%
Procedures					
Region					
	Northern	179 761	3.13%	1 442 382	4.99%
	Northeastern	896 916	15.62%	5 551 764	19.22%
	Southeastern	3 071 586	53.49%	15 271 343	52.88%
	Southern	1 236 067	21.53%	4 285 803	14.84%
	West-central	357 586	6.23%	2 327 703	8.06%
	Brazil	5 741 916	100.00%	28 878 995	100.00%
Surgeries					
Region					
	Northern	13 676	2.57%	13 774	2.33%
	Northeastern	98 475	18.52%	442 540	74.81%
	Southeastern	239 747	45.10%	81 777	13.82%
	Southern	140 536	26.44%	43 469	7.35%
	West-central	39 192	7.37%	9 961	1.68%
	Brazil	531 626	100.00%	591 521	100.00%
ADMISSIONS					
DEATHS					
		Quantity	Percentage	Quantity	Percentage
Morbidity					
	Stroke	357 040	26.72%	52 239	36.75%
	Hypertensive diseases	153 048	11.45%	2 920	2.05%
	Rheumatic diseases	19 125	1.43%	1 329	0.93%
	Acute myocardial infarction	242 143	18.12%	24 753	17.41%
	Heart failure	399 416	29.89%	43 906	30.89%
	Congenital malformations	33 939	2.54%	2 370	1.67%
	Conduction disorders and arrhythmias	131 761	9.86%	14 640	10.30%
	Total	1 336 472	100.00%	142 157	100.00%

continuation

Region					
	Northern	77 577	5.80%	8 578	6.03%
	Northeastern	327 515	24.51%	35 749	25.15%
	Southeastern	563 293	42.15%	63 609	44.75%
	Southern	270 995	20.28%	23 624	16.62%
	West-central	97 092	7.26%	10 597	7.45%
	Total	1 336 472	100.00%	142 157	100.00%
Sex					
	Male	704 163	52.69%	73 227	51.51%
	Female	632 309	47.31%	68 930	48.49%
	Total	1 336 472	100.00%	142 157	100.00%
Race/Skin color					
	White	491 422	36.77%	48 962	34.44%
	Black	58 968	4.41%	6 301	4.43%
	Mixed	435 848	32.61%	46 276	32.55%
	Yellow	28 768	2.15%	2 764	1.94%
	Native	1 025	0.08%	107	0.08%
	No information	320 441	23.98%	37 747	26.55%
	Total	1 336 472	100.00%	142 157	100.00%
Age group (years)					
	0-19	44 658	3.34%	3 241	2.28%
	20-59	415 122	31.06%	29 245	20.57%
	60+	876 692	65.60%	109 671	77.15%
	Total	1 336 472	100.00%	142 157	100.00%
Type of care					
	Elective	104 229	7.80%	5 454	3.84%
	Urgent	1 232 243	92.20%	136 703	96.16%
	Total	1 336 472	100.00%	142 157	100.00%

ABPM: ambulatory blood pressure monitoring.

Figure 1B depicts the numbers of admissions and in-hospital deaths recorded, considering all morbidities studied. In addition, the estimates for 2020 (dotted lines), calculated by using data from 2016 to 2019, are also shown. The graph shows the same trend towards an increase observed in the previous graph but not confirmed in the year 2020, when a steep decline is observed. Regarding the number of deaths, the projected trend would be that of maintenance, contrasting with the intense reduction in the number of in-hospital deaths recorded in the months of March to May 2020.

Figure 1C illustrates the in-hospital fatality rate due to CVD in general, showing a drastic increase in the in-hospital fatality rate in 2020 as compared to those recorded in previous years. In this case, the variation is in the opposite direction to that observed for the admissions and in-hospital deaths, which decreased in 2020.

That analysis was replicated for each type of procedure and surgery, as well as for the number of admissions, in-hospital deaths and in-hospital fatality rate for each pathology studied. Those

results are summarized in Tables 2 and 3, which show data from 2019 and 2020, the percent difference between these years, the value projected for 2020 (which indicates the trend from 2016 to 2019), the confidence interval, and the p-value of that projection. The results according to age group are shown in the supplementary material.

Diagnostic and Surgical Procedures

Table 2 shows the comparison of the number of diagnostic and surgical procedures performed in March, April, and May of 2019 and 2020, with a total drop of 45% in all procedures studied in 2020. The procedures with the most significant reductions were as follows: ABPM (74% reduction), exercise test (59%), and 24-hour Holter (51%). Electrocardiography and echocardiography had a decrease of 41% and 42%, respectively. Cardiac catheterization and pacemaker implantation had the smallest decline, 27% and 11%, respectively.

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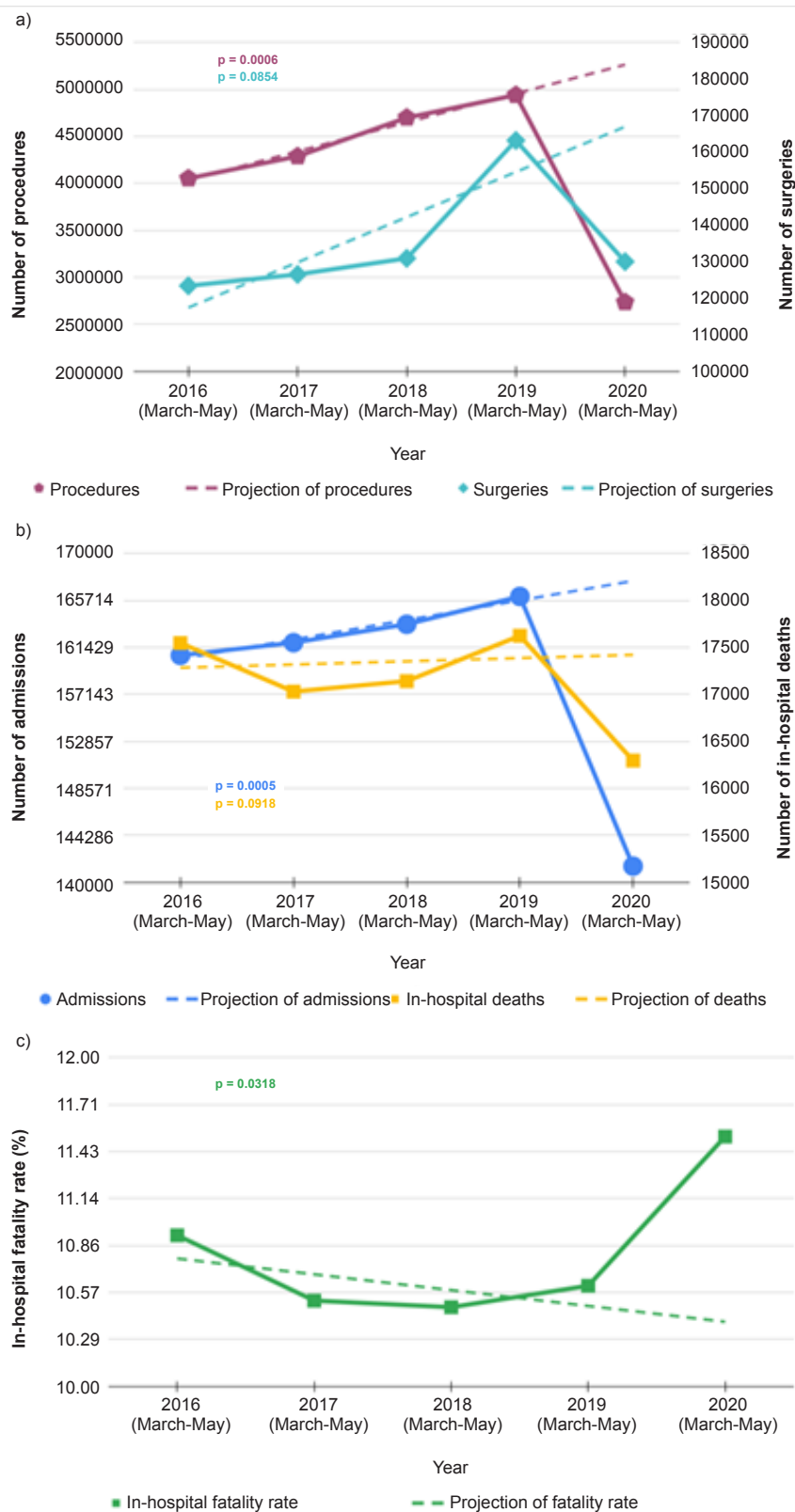


Figure 1 – Analysis of the trend in: (a) the number of procedures and surgeries; (b) the number of admissions and deaths; and (c) in-hospital fatality rate in March to May of 2016 to 2020. *p*-value calculated from the difference between the value projected and the value recorded in 2020 using Student *t* distribution.

Table 2 – Statistical analysis of the reduction in the number of procedures and surgeries in March to May of 2019 and 2020 and their comparison

	Number of procedures		Percent difference 2020 - 2019	Number of procedures estimated for 2020 (March-May)	Confidence interval (95% CI)	p-value
	2019 March-May	2020 March-May				
Procedures						
Adult cardiac catheterization	61 502	44 652	-27%	63 823	68 921 – 58 724	0.0041
Echocardiography	530 448	307 221	-42%	568 014	599 663 – 536 364	0.0009
Electrocardiography	3 624 680	2 153 969	-41%	3 795 712	3 952 567 – 3 638 856	0.0005
Pacemaker implantation	5 993	5 315	-11%	6 129	6 711 – 5 546	0.0276
ABPM	498 923	127 730	-74%	609 445	748 875 – 470 014	0.0048
Holter monitoring	79 792	38 815	-51%	84 592	93 971 – 75 212	0.0024
Exercise test	137 678	56 501	-59%	134 673	149 970 – 119 375	0.0022
All	4 939 016	2 734 203	-45%	5 262 388	5 516 598 – 5 008 177	0.0006
Surgeries						
Cardiovascular	23 907	20 744	-13%	24 045	26 897 – 21 191	0.0388
Vascular	101 694	83 786	-18%	104 654	159 586 – 49 720	0.1914
Endovascular	37 547	25 461	-32%	38 208	45 145 – 31 269	0.0165
All	163 148	129 991	-20%	166 906	218 270 – 115 540	0.0854
TOTAL	5 102 164	2 864 194	-44%	5 429 294	5 670 710 – 5 187 876	0.0005

ABPM: ambulatory blood pressure monitoring. Confidence intervals and p-values calculated by using Student t distribution, considering the differences between the value projected and the value recorded in 2020.

The total number of surgeries performed in March, April, and May 2020 decreased by 20% as compared to the previous year, which was not statistically significant ($p=0.0854$). However, when considering only cardiovascular and endovascular surgeries, declines of 13% and 32%, respectively, were observed, both with statistical significance ($p<0.05$).

Admissions

Regarding the admissions due to cardiovascular diseases in March, April, and May 2020, a 15% reduction was observed as compared to the same period of the previous year (Table 3). Data from all diseases analyzed individually also showed a statistically significant reduction. The greatest differences were in admissions due to hypertensive diseases, followed by those due to rheumatic diseases, with 33% and 29% reductions, respectively. It is worth noting that admissions due to AMI had the smallest reduction (4%).

In general, all diseases showed a decrease in admissions from 2019 to 2020 for all age groups. The following are worthy of note: AMI, whose difference in admissions had statistical significance only for the elderly group; heart failure, in which the extreme age groups (child/adolescent and elderly) had the greatest impacts; and conduction disorders and other arrhythmias, which showed statistically significant reduction only for the elderly. When considering admissions from stroke, the adults and the elderly had significant reductions (11% and

12%, respectively). Regarding admissions from hypertensive diseases, all age groups had statistically significant reductions.

In-hospital Deaths and In-hospital Fatality Rate

The absolute number of deaths due to CVD decreased by 8% from March to May 2020 as compared to the same period in 2019 (Table 3). The deaths related to hypertensive diseases in the age group 20-59 years had a 21% increase in 2020 ($p<0.05$; supplementary material).

Regarding the general fatality rates, there was an overall 9% increase when comparing the same months of 2019 and 2020. Except for AMI, whose fatality rate decreased by 5%, all other pathologies had an increase in fatality rates. Regarding the pathologies individually, hypertensive diseases and heart failure stood out, with 29% and 8% increases in their in-hospital fatality rates, respectively, from 2019 to 2020 ($p<0.05$).

When considering the age groups, the in-hospital fatality increase in the admissions due to CVD was statistically significant only among adults. Considering the diseases individually, it is worth noting that the in-hospital fatality increase due to hypertensive diseases was statistically significant only for adults. Regarding heart failure, adults and elderly showed statistical difference in that rate ($p<0.05$; Tables 2 and 3 of the supplementary material).

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Table 3 – Statistical analysis of the number of admissions, in-hospital deaths, and in-hospital fatality rate in March to May of 2019 and 2020 and their comparison

	Data recorded in		Percent difference 2020 - 2019	Estimates for 2020 March- May	Confidence interval (95% CI)	p-value
	2019 March - May	2020 March - May				
Admissions						
Stroke	45 214	39 900	-12%	46 199	48 586 – 43 811	0.0082
Hypertensive diseases	18 278	12 229	-33%	18 053	20 331 – 15 773	0.0088
Rheumatic diseases	2403	1701	-29%	2 266	2683 – 1847	0.0294
Acute myocardial infarction	31 566	30 298	-4%	33 084	35 550 – 30 616	0.0405
Heart failure	47 250	39 667	-16%	46 077	49 847 – 42 305	0.0191
Cardiovascular malformations	4489	3692	-18%	4602	4883 – 4320	0.0055
Conduction disorders and cardiac arrhythmias	16 875	13 977	-17%	17 212	18 316 – 16 107	0.0067
Cardiovascular comorbidities	166 075	141 464	-15%	167 491	169 772 – 165 209	0.0005
In-hospital deaths						
Stroke	6411	5871	-8%	6363	7364 - 5361	0.1439
Hypertensive diseases	336	289	-14%	309	361 - 256	0.1926
Rheumatic diseases	180	144	-20%	161	262 - 58	0.3414
Acute myocardial infarction	3081	2805	-9%	3094	3500 - 2686	0.0872
Heart failure	5356	4845	-10%	5212	5612 - 4811	0.0579
Cardiovascular malformations	307	288	-6%	297	382 - 210	0.3995
Conduction disorders and cardiac arrhythmias	1952	2053	5%	1986	2582 - 1388	0.3863
Cardiovascular comorbidities	17 623	16 295	-8%	17 420	19 062 – 15 777	0.0918
In-hospital fatality rate						
Stroke	14.18	14.71	4%	13.72%	15.33 - 12.10	0.1067
Hypertensive diseases	1.84	2.36	29%	1.72%	2.11 - 1.34	0.0198
Rheumatic diseases	7.49	8.47	13%	7.08%	10.19 - 3.97	0.1616
Acute myocardial infarction	9.76	9.26	-5%	9.20%	10.21 - 8.18	0.4363
Heart failure	11.34	12.21	8%	11.31%	12.01 - 10.60	0.0322
Cardiovascular malformations	6.84	7.80	14%	6.40%	8.26 - 4.54	0.0798
Conduction disorders and cardiac arrhythmias	11.57	14.69	27%	11.57%	14.90 - 8.24	0.0559
Cardiovascular comorbidities	10.61	11.52	9%	10.39%	11.26 - 9.52	0.0318

Confidence intervals and p-values calculated by using Student t distribution, considering the differences between the value projected and the value recorded in 2020.

Discussion

This study shows a reduction in the cardiovascular care provided to the Brazilian population by the SUS during the COVID-19 pandemic, which resulted in both a reduction in the number of hospital admissions for CVD and an increase in the in-hospital fatality rate from those diseases.

Our results are similar to those of a study carried out in Italy during 7 days in March 2020, which showed a 13.3% reduction in the proportion of patients with AMI as compared

to that same week of 2019. In addition, that study reported a 39.2% increase in acute coronary syndromes and a 31.5% increase in the time elapsed from medical contact to coronary revascularization.¹²

In our study, regarding the number of admissions, there was a reduction for all morbidities and age groups analyzed, mainly in April and May, possibly because of the COVID-19 pandemic. Other studies carried out in different countries have reported similar findings.^{13–15} The population's fear of

contracting the virus and the systematization of the healthcare, prioritizing the pandemic, justify that initial impact.^{16,17} That reduction has also been reported for other diseases, as shown by the studies on stroke in Italy¹⁸ and China.¹⁹

The reassignment of human resources in the fight against COVID-19 was similar in several countries, despite the heterogeneity of their health systems.¹² Some countries, such as Australia and New Zealand, to prepare hospitals to provide healthcare to a large number of patients with COVID-19, kept the delivery of surgical care limited to emergency or high-priority elective cases.²⁰ In a hospital in Northern Italy, one of the epicenters of the pandemic in that country, the planned surgical activities were interrupted to increase the number of intensive care physicians available to patients with COVID-19, and the outpatient activities were cut to half.²¹ This rearrangement in the healthcare model was expected to have an impact on the mortality from other diseases, whose usual healthcare delivery flow was reduced, favoring clinical decompensations, diagnostic delay, and disease progression.

Despite the reduction in absolute numbers of in-hospital deaths, there was an increase in the in-hospital fatality rate of admissions due to CVD. That reduction in the number of deaths might have resulted from the lack of proper reporting and the deficient structure of the health system to properly designate the COVID-19-related cause of death as cardiovascular. The interaction between COVID-19 and the cardiovascular system is currently well known, after 7 months of disease. COVID-19 is related to a high prevalence of cardiac injury, arrhythmias, myocarditis, acute coronary syndrome, heart failure, cardiogenic shock, and thromboembolic events.²² The increased fatality in admissions due to CVD reflects the potential severity of COVID-19 in CVD and the possible patient's delay in searching medical care, being then hospitalized in more severe conditions. The increased fatality of patients admitted due to CVD has reached the most economically-active part of the population (20-59 years), adding more concern to the ongoing economic crisis. Although some studies have observed a similar impact of the pandemic on hospital care,^{13,15,20-23} ours might be one of the first to demonstrate an increase in the in-hospital fatality rate due to CVD.¹²

This study has the limitation of assessing only one part of the Brazilian population, the one with access to only the SUS-provided healthcare. Thus, our data cannot be extrapolated to the whole population of Brazil. It is worth noting that the impact demonstrated on the fatality of Brazilians might be overestimated, because the population cared for at the SUS, being socioeconomically disadvantaged, has a poorer control

of cardiovascular risk factors, in addition to having access to medication of poorer quality and in an unsatisfactory manner.²⁴ Such factors on their own make that population more vulnerable to clinical decompensation, with consequent higher in-hospital fatality. Moreover, the restriction of elective admissions might have influenced in-hospital fatality, although that type of healthcare represents only 7.80% of the total of admissions (Table 1). It is worth noting the shortness of the period analyzed (3 months). Therefore, further studies should validate these findings and compare them to those of other periods.

Conclusions

Ours is the first study to assess the impact on cardiovascular health at the SUS across Brazil during the COVID-19 pandemic. These data support the concern that healthcare delivery might have been postponed or reduced during the COVID-19 pandemic.

Author Contributions

Conception and design of the research, Acquisition of data e Statistical analysis: Normando PG, Fonseca GA, Rodrigues REF, Oliveira VA, Melo M; Analysis and interpretation of the data and Writing of the manuscript: Normando PG, Araujo-Filho JA, Fonseca GA, Rodrigues REF, Oliveira VA, Hajjar LA, Almeida ALC, Bocchi EA, Salemi VMC, Melo M; Critical revision of the manuscript for intellectual content: Araujo-Filho JA, Hajjar LA, Almeida ALC, Bocchi EA, Salemi VMC, Melo M.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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*Supplemental Materials

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Avoidable Cardiovascular Events: A Serious Side Effect of the COVID-19 Pandemic

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Short Editorial related to the article: Reduction in Hospitalization and Increase in Mortality Due to Cardiovascular Diseases during the COVID-19 Pandemic in Brazil

Soon after the beginning of the COVID-19 pandemic, a general feeling arose among the doctors: many patients would have poor outcomes due to delays in seeking medical services for fear of infection. Patients with acute myocardial infarction, decompensated heart failure or stroke would stay at home or go to the hospital late in the course of the event. Investigation of potentially serious diseases, such as cancer, would be postponed. Besides, healthcare collapse would prove to be a contributor to inadequate care of non-COVID-19 diseases.

It took some months for the researchers to gather data on the nuances of this phenomenon. Several publications have confirmed the expectations, shedding light on an aspect that must be discussed and disseminated.

In this context, this issue of ABC publishes an analysis of the impact of the first months of the pandemic on the number of medical procedures, hospital admissions, and in-hospital deaths due to cardiovascular diseases in the setting of the Brazilian public healthcare service.¹ The numbers expected for March to May 2020, based on the trends from 2016 to 2019, were confronted with the numbers observed during the pandemic. The main results indicate that the number of procedures, surgeries, hospital admissions, and in-hospital deaths was much lower than expected. The authors describe a 15% decrease in hospital admissions due to cardiovascular diseases. In-hospital deaths due to cardiovascular diseases also dropped, but not to the same extent (-8%). As a consequence, in-hospital mortality increased by 9%.¹

The reduced number of cardiac procedures and hospital admissions due to cardiovascular urgencies is consistent with other reports from Brazil and other countries.²⁻⁴ This observation, per se, would not be a problem if relevant outcomes, such as deaths, post-myocardial infarction heart failure and post-stroke disabilities had not increased. Unfortunately, this is not the case. Brant et al.⁵ have published a comprehensive analysis of excess cardiovascular mortality from March to May 2020 in the six Brazilian capitals with

the highest number of COVID-19 fatalities. The authors found an excess in total cardiovascular deaths in most cities, especially due to unspecified cardiovascular causes, which were correlated with an increase in home deaths.⁵

Concerns about indirect, harmful consequences of the pandemic are not restricted to cardiovascular diseases. Several publications have highlighted a reduced demand for cancer services, and a lower number of diagnostic exams and therapeutic procedures for cancer during the pandemic.⁶⁻⁹

Therefore, the collateral damage of the COVID-19 pandemic is clear and alarming, and strategies to minimize avoidable events must be developed and implemented. This is especially true in the setting of cardiovascular diseases, the leading cause of death in the world and in Brazil.¹⁰

Obviously, the ideal solution is to control the pandemic itself, which takes time and will depend on the success of the vaccination program, which is always threatened by the emergence of new variants of the severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2). As long as the community transmission of the virus is at high levels, other initiatives may help.

Firstly, it is mandatory to make doctors and patients aware of the danger of delaying diagnosis and treatment of cardiovascular diseases, malignancies, and other pathological processes. Physicians should master the frequently hard task of balancing the benefits and risks of referring patients to diagnostic procedures and hospital admissions. The correct discernment on the urgency depends on a mixture of continuing education, training, and common sense. Public campaigns targeting lay people may also be useful.

Secondly, healthcare services must be prepared to minimize risks to patients and healthcare professionals during the pandemic. Medical societies have a role in guiding the health providers to safely perform procedures, such as the Brazilian Society of Cardiology has done by issuing documents with specific recommendations.¹¹⁻¹³ Teaching, reference hospitals can also contribute by sharing their experience and protocols that may be used by smaller centers.¹⁴

Thirdly, we should take advantage of remote healthcare to partially fill the gap of restricted access to medical assistance in these pandemic times. Intelligent use of telemedicine,¹⁵ home visits by the health team, blood collection at home, and electrocardiogram teletransmission are some examples of practices that may be performed.

In conclusion, it is now clear that the impacts of the COVID-19 pandemic go far beyond deaths due to viral pneumonia and socio-economic aspects. Patients are more reluctant and have postponed medical investigations, largely

Keywords

COVID-19; Betacoronavirus; Pandemics; Myocardial Infarction; Heart Failure; Cardiovascular Diseases/mortality; Vaccination.

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due to the fear of being infected with SARS-CoV-2. Although understandable from the patient's perspective, these attitudes pose high risks, especially when it comes to cardiovascular

diseases and cancer. Efforts must be made to limit preventable events and to minimize the tragic consequences of this ongoing pandemic or other disasters that might affect us in the future.

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Prognostic Value of Lung Ultrasound for Clinical Outcomes in Heart Failure Patients: A Systematic Review and Meta-Analysis

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Abstract

Background: There is conflicting information about whether lung ultrasound assessed by B-lines has prognostic value in patients with heart failure (HF).

Objectives: To evaluate the prognostic value of lung ultrasound assessed by B-lines in HF patients.

Methods: Four databases (PubMed, EMBASE, Cochrane Library, and Scopus) were systematically searched to identify relevant articles. We pooled the hazard ratio (HR) and 95% confidence interval (CI) from eligible studies and carried out heterogeneity, quality assessment, and publication bias analyses. Data were pooled using a fixed-effects or random-effect model. A p value < 0.05 was considered to indicate statistical significance.

Results: Nine studies involving 1,212 participants were included in the systematic review. B-lines > 15 and > 30 at discharge were significantly associated with increased risk of combined outcomes of all-cause mortality or HF hospitalization (HR, 3.37, 95% CI, 1.52-7.47; $p = 0.003$; HR, 4.01, 95% CI, 2.29-7.01; $p < 0.001$, respectively). A B-line > 30 cutoff at discharge was significantly associated with increased risk of HF hospitalization (HR, 9.01, 95% CI, 2.80-28.93; $p < 0.001$). Moreover, a B-line > 3 cutoff significantly increased the risk for combined outcomes of all-cause mortality or HF hospitalization in HF outpatients (HR, 3.21, 95% CI, 2.09-4.93; $I^2 = 10\%$; $p < 0.00001$).

Conclusion: B-lines could predict all-cause mortality and HF hospitalizations in patients with HF. Further large randomized controlled trials are needed to explore whether dealing with B-lines would improve the prognosis in clinical settings. (Arq Bras Cardiol. 2021; 116(3):383-392)

Keywords: Lung/ultrasonography; B Lines; Prognosis; Heart Failure; Review; Meta-Analysis.

Introduction

Heart failure (HF) remains the leading cause of hospitalization in recent decades due to its high prevalence, morbidity, and mortality rates.¹ Pulmonary congestion can predict both mortality and morbidity in patients with HF,² and decongestion is one of the primary goals of HF management in patients during hospitalization.³

Lung ultrasound (LUS) is a simple, patient-friendly, reliable, sensitive tool to detect pulmonary congestion assessed by B-lines.^{4,5} B-line is a kind of comet-tail artifact that appears as discrete laser-like vertical hyperechoic reverberation artifacts, arises from the pleural line, extends to the bottom of the screen, moves synchronously with lung sliding and erases A-lines.⁶ B-lines represent thickened interlobular septa. The sum of B-lines in all scanned spaces yields a score denoting the extent of extravascular

fluid in the lung, and zero is defined as a complete absence of B-lines in the investigated area.⁷ Bedside LUS has been recognized in a scientific statement of the European Society of Cardiology as one of the key elements in the measurement of clinical congestion since 2010,⁸ and was recommended in 2015 to assess pulmonary edema in patients with suspected acute HF.⁹

An ultrasound-based technique to evaluate pulmonary congestion has served as an aid in the differentiating causes of acute dyspnea mainly in accident and emergency setting,¹⁰ but also as an evaluation in other conditions.^{11,12} Animal studies have supported the use of thoracic ultrasonography and detection of B-lines as techniques for diagnosing cardiogenic pulmonary edema in dogs.¹³ Also, LUS has been identified to be a reproducible as well as a reliable tool to detect pulmonary congestion, to identify the onset of HF decompensation, and to evaluate the therapeutic efficiency for this syndrome in mice.¹⁴ B-lines provide a useful biomarker to evaluate the time course of extra-vascular lung water changes after interventions. After adequate HF medical treatment, B-line pattern mostly clears, which represents an easy-to-use alternative bedside diagnostic approach to evaluate pulmonary congestion in patients with decompensated HF.¹⁵ A higher B-line number was associated with an increased risk of morbidity and mortality in other disease settings such as acute coronary syndrome¹⁶ and dialysis.¹⁷ However, its efficacy in patients with HF has not been well established.

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Owing to the limited number of clinical studies on this topic, we believed it worthwhile to carefully evaluate the accumulated evidence. In the present meta-analysis, we systematically examined the prognostic value of pulmonary congestion conveyed by B-lines in patients with HF.

Methods

Literature search

This study was performed under the guidance of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.¹⁸ The PRISMA 2009 checklist was listed in the supplementary file. This was registered with PROSPERO (CRD 42019138780). We searched PubMed, EMBASE, Cochrane Library and Scopus from their start date up to July 2019 to identify eligible studies, using the keywords and/or medical subject heading terms: “B lines” or “lung ultrasound” or “ultrasound lung comets” or “pulmonary congestion”) and (“heart failure” or “cardiac dysfunction” or “cardiac failure” or “cardiac insufficiency”. No language restrictions were used. The references of relevant literatures were also searched to find more eligible studies.

Study inclusion and exclusion criteria

The inclusion criteria in this review and meta-analysis were as follows with reference to participants, interventions, comparisons, outcomes, and study design (PICOS) as described on PRISMA protocol:

- (1) enrollment of patients with HF (either of new HF or worsening chronic heart failure requiring hospitalization);
- (2) use of ultrasound lung comets to assess pulmonary congestion in HF patients;
- (3) reported hazard ratios (HR) for possible outcome measures (all-cause mortality, hospitalization by HF, or combined outcomes); and
- (4) follow-up studies, including post hoc analysis of randomized clinical trials.

The exclusion criteria were:

- (1) reviews, meta-analyses, non-human study, letters, case reports, and conferences; and
- (2) studies that do not provide results on patients with HF.

Data extraction and quality assessment

Two investigators (Y.W. and X.P.) independently examined all titles, abstracts and full-text articles extracted from databases for potentially relevant studies. Any discrepancies were resolved by discussion among all authors. Data extracted from each study were: first author's last name, year of publication, country where the study was carried out, the types of study involved, the number of participants, follow-up periods, and outcomes of interest. A Newcastle-Ottawa Quality scale (NOS) ranging from zero (lowest) to nine (highest) was applied to assess the methodological quality for cohort studies, as recommended by the Cochrane Non-Randomized Studies Methods Working Group.¹⁹ A score of ≥ 5 was considered

to be of high quality. In addition, the Quality In Prognosis Studies (QUIPS) tool was applied to examine bias and validity in articles of prognostic factors.²⁰

Statistical analysis

The RevMan 5.3 (The Cochrane Collaboration, Oxford) and Stata version 11 (StataCorp) software were properly used in all statistical analyses. The Cochrane Q and the I^2 statistics were calculated to assess heterogeneity across the studies. The Cochrane Q-statistic test with a p-value ≤ 0.05 was considered statistically significant. I^2 values of 25, 50, and 75% corresponded to low, moderate, and high degrees of heterogeneity, respectively.²¹ If I^2 was greater than 50%, we chose to use a random-effects model (DerSimonian and Laird's method) to combine the results and if I^2 was lower than 50% we created a fixed-effects model (Mantel-Haenszel's method).²² The use of a random-effects model was also considered when the number of studies was small. We combined the HR across studies using generic inverse-variance weighting and the 95% confidence interval (CI) for each outcome. The overall log (HR) with its 95%CI was used as the summary of the overall effect size. In addition, subgroup analyses were carried out based on numbers of B-lines at discharge in the included studies. Sensitivity analyses were conducted by excluding one study involved in this review and meta-analysis at a time to reflect the effect of the specific data set on the overall HR. Publication bias was quantitatively analyzed by the Begg's rank correlation test²³ and the Egger's linear regression test.²⁴ A p-value < 0.05 was considered to indicate statistical significance.

Results

Search Results

Our search strategy was outlined in Figure 1. Our literature search identified 847 potentially relevant articles. We excluded 455 studies based on the screening of titles and abstracts of those papers. Fifty-eight articles were excluded after going through full-text review, and finally the remaining 9 articles²⁵⁻³³ were included in the meta-analysis.

Study characteristics and quality assessment

The 9 studies included here ranged from 54 to 342 patients, with a final population of 1,212 patients. Of these, seven studies were carried out in Europe and one in the United States. Table 1 represents the baseline characteristics of the articles included in this meta-analysis. Of those, there were eight prospective studies^{25-30,32,33} and one retrospective one.³¹ Five out of nine studies^{27,29,30,32,33} enrolled a total of 792 HF outpatients and the other four studies enrolled 420 patients hospitalized for HF. In addition, four studies^{26,28,31,32} had follow-up durations of 3 or 4 months and the other five studies had follow-up periods of no less than 6 months. Data for HF hospitalization was available for only two studies, while most studies reported data on combined outcomes of death or HF hospitalization. The mean age of patients ranged from 53 to 81 years old. The patients in the included studies were predominately male. The main patients' characteristics were

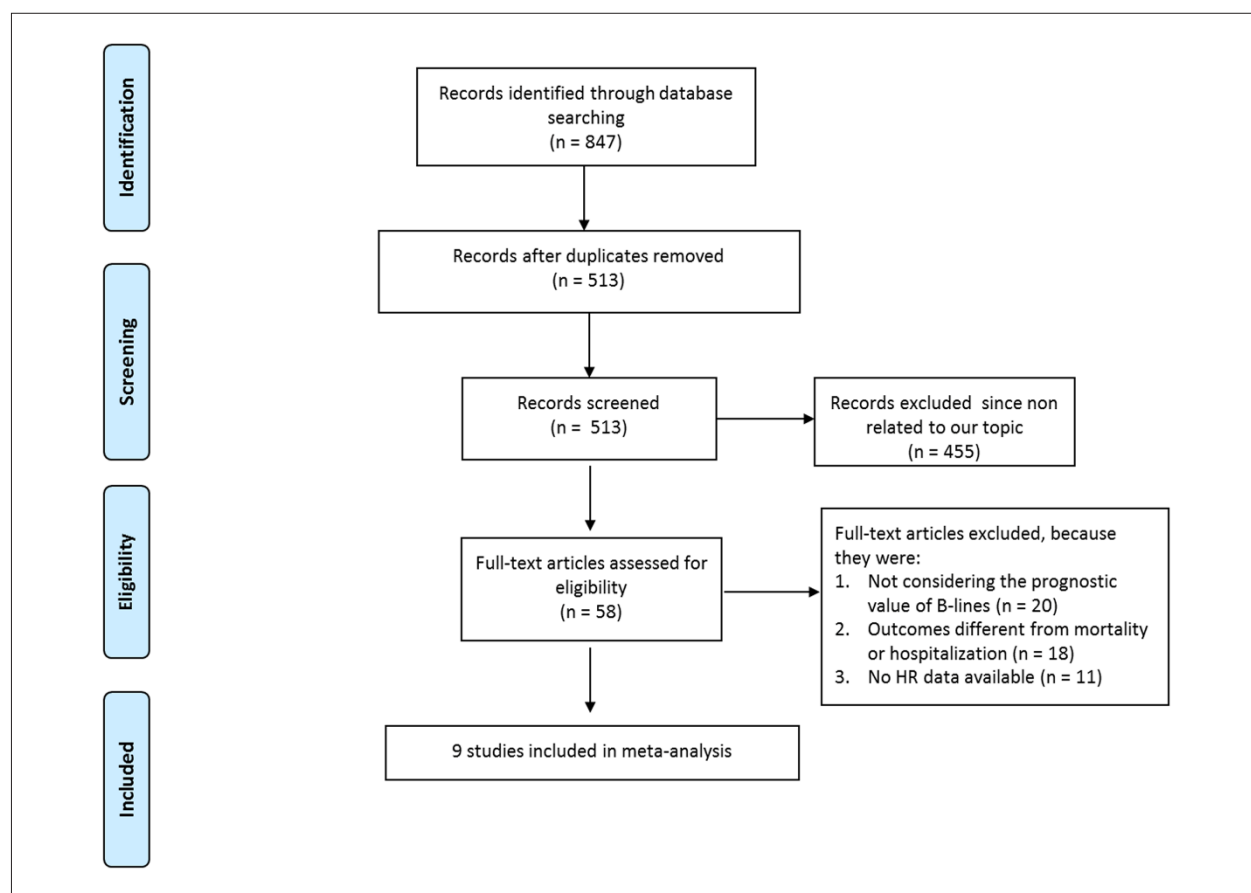


Figure 1 – Flow diagram of selection process.

summarized in Table 2. According to the NOS shown in Table 3, all of the included studies were considered to be of high-quality. However, four articles were given a score of 8 due to relatively short follow-up duration. Table 4 showed the overall quality assessment of the included studies using the QUIPS tool. The seven eligible articles were usually at low to moderate risk of bias in terms of study attrition, prognostic factor and outcome measurement, study participation, definition of outcomes and statistical analysis and reporting. Furthermore, some studies were at high risk of bias because they reported unadjusted analysis or did not report adjusted analysis.

Discharge B-lines and combined outcomes of all-cause mortality or HF hospitalization

Three studies^{26,28,31} reported the association between discharge B-lines and combined outcomes of death or HF hospitalization. Pooled estimates showed that there was a strong tendency toward the association between discharge B-lines and increased risk of combined outcomes of death or HF hospitalization (HR, 1.08, 95% CI, 0.99-1.19; $I^2 = 91\%$; $p = 0.09$; Figure 2). Subgroup analysis^{28,31} based on numbers of B-lines at discharge revealed that B-lines > 15 at discharge was significantly associated with increased risk of death or HF hospitalization (HR, 3.37, 95% CI, 1.52-7.47; $I^2 = 0\%$; $p = 0.003$; Figure 3). Also, B-lines > 30 at discharge

significantly correlated with increased risk of combined outcomes of death or HF hospitalization (HR, 4.01, 95% CI, 2.29-7.01; $I^2 = 0\%$; $p < 0.001$; Figure 3). Furthermore, sensitivity analysis restricted to two prospective studies^{26,28} demonstrated that B-lines > 30 significantly correlated with combined outcomes of death or HF hospitalization (HR, 3.46, 95% CI, 1.86-6.47; $I^2 = 0\%$; $p = 0.0001$). Sensitivity analysis by omitting any single study yielded similar results.

Discharge B-lines and HF hospitalization

Two studies^{25,26} reported the association between discharge B-lines and HF hospitalization. Overall estimates demonstrated that discharge B-lines were significantly associated with HF hospitalization (HR, 1.05, 95% CI, 1.01-1.09; $p = 0.01$; Figure 4), with substantial heterogeneity ($I^2 = 87\%$). Furthermore, subgroup analysis indicated that B-lines > 30 at discharge significantly increased risk of HF hospitalization (HR, 9.01, 95% CI, 2.80-28.93; $p < 0.001$; Figure 4), with no heterogeneity ($I^2 = 0\%$).

B-lines and combined outcomes of all-cause mortality or HF hospitalization in HF outpatients

Five studies^{27,29,30,32,33} assessed the association between B-lines and combined outcomes of death and HF

Table 1 – Key characteristics of the included studies

First Author	Publication year	Country	Type of study	Study participants	Number of patients, n	Follow-up periods	All-cause deaths, n	HF hospitalization, n	All-Cause death or HF hospitalization, n	Reported outcomes	Quality of study	Level of significance adopted
Gargani ²⁵	2015	Italy	Prospective cohort	Inpatients	100	6 months	4	14	NA	HF hospitalization	9	p <0.05
Coiro ²⁶	2015	France	Prospective cohort	Inpatients	60	3 months	10	15	18	All-cause death or HF hospitalization	8	p <0.05
Gustafsson ²⁷	2015	Sweden	Prospective cohort	Outpatients	104	6 months	14	18	24	All-cause death or HF hospitalization	9	p <0.05
Cogliati ²⁸	2016	Italy	Prospective cohort	Inpatients	150	100 days	11	23	34	All-cause death or HF hospitalization	8	p <0.05
Platz ²⁹	2016	America (USA?)	Prospective cohort	Outpatients	195	6 months	15	48	54	All-cause death or HF hospitalization	9	p <0.05
Villanueva ³⁰	2016	Spain	Prospective cohort	Outpatients	54	6 months	NA	18	NA	All-cause death or HF hospitalization	9	NR
Coiro ³¹	2016	France	Retrospective cohort	Inpatients	110	3 months	16	26	33	All-cause death or HF hospitalization	8	p <0.05
Miglioranza ³²	2017	Brazil	Prospective cohort	Outpatients	97	4 months	3	23	NA	All-cause death, HF hospitalization, MACE	8	p <0.05
Pelliconi ³³	2018	United Kingdom	Prospective cohort	Outpatients	342	12 months	25	35	NA	All-cause death or HF hospitalization	9	p <0.05

HF: heart failure; MACE: major adverse cardiac events; NA: not applicable; NR: not reported.

Table 2 – Baseline characteristics of patients from the included studies

Studies	Age, mean/median, years	Men, %	LVEF, mean/median, %	E/e' ratio	CAD, %	HTN, %	DM, %	ACE-I/ARB, %	β-blockers, %	MRA, %	Diuretics, %	Digoxin, %
Gargani 2015	70	73	37	NA	NA	57	39	63	60	60	100	NA
Coiro 2015	72	68	38	19.11 ± 9.5	32	NA	NA	NA	NA	NA	NA	NA
Gustafsson 2015	72	72	NA	NA	40	57	24	95	89	31	78	NA
Cogliati 2016	81	42	48	NA	42	62	34	69	66	39	96	24
Platz 2016	NA	61	32	NA	NA	71	49	67	89	29	92	21
Maria 2016	79	54	NA	NA	33	94	54	72	57	NA	100	17
Coiro 2016	73	55	39	16 ± 1	46	NA	NA	NA	NA	NA	NA	NA
Miglioranza 2017	53	61	28	17 (13.30)	30	53	23	66	95	53	62	50
Pellicori 2018	NA	67	NA	NA	49	55	29	85	73	49	75	NA

LVEF: left ventricular ejection fraction; CAD: coronary artery disease; HTN: hypertension; DM: diabetes mellitus; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; MRA: mineralocorticoid receptor antagonist; NA: not applicable.

Table 3 – Study quality assessment using the Newcastle-Ottawa Scale for cohort studies

First author, year of publication (reference)	Selection				Outcome				Total score
	Representativeness of exposed cohort	Selection of nonexposed cohort	Ascertainment of exposure	Outcome of interest absent at start of study	Comparability	Assessment of outcome	Follow-up long enough for outcomes to occur	Adequacy of follow-up	
Gargani 2015	*	*	*	*	**	*	*	*	9
Coiro 2015	*	*	*	*	**	*	-	*	8
Gustafsson 2015	*	*	*	*	**	*	*	*	9
Cogliati 2016	*	*	*	*	**	*	-	*	8
Platz 2016	*	*	*	*	**	*	*	*	9
Villanueva 2016	*	*	*	*	**	*	*	*	9
Coiro 2016	*	*	*	*	**	*	-	*	8
Miglioranza 2017	*	*	*	*	**	*	-	*	8
Pellicori 2018 ³³	*	*	*	*	**	*	*	*	9

Asterisks are the star ratings per Newcastle-Ottawa Scale; * and ** indicate the highest ratings for these categories.

hospitalization in HF outpatients. The pooled HRs showed that B-lines > 3 significantly increased the risk for combined outcomes of death or HF hospitalization in HF outpatients (HR, 3.21, 95% CI, 2.09-4.93; $I^2 = 10\%$; $p < 0.00001$; Figure 5). Sensitivity analysis restricted to three studies^{27,30,32,33} conducted outside of America demonstrated that B-lines > 3 significantly correlated with combined outcomes of death or HF hospitalization (HR, 2.96, 95% CI, 1.69-5.16; $I^2 = 22\%$; $p < 0.001$). Sensitivity analysis was further conducted

by omitting any single study that did not significantly alter the overall effect estimates.

Publication bias

Egger's and Begg's tests suggested no significant publication bias of combined outcomes of death or HF hospitalization in both in- (Egger $p = 0.15$ and Begg $p = 1.00$) and outpatients (Egger $p = 0.33$ and Begg $p = 1.0$).

Table 4 – Study-level quality assessment using the Quality in Prognosis Studies tool

Study	Study participation	Study attrition	Prognostic factor measurement	Outcome measurement	Study confounding	Statistical analysis and reporting
Gargani 2015 ²⁵	L	L	L	L	H	L
Coiro 2015 ²⁶	L	M	L	L	H	L
Gustafsson 2015 ²⁷	L	L	L	L	L	L
Cogliati 2016 ²⁸	L	L	L	L	H	L
Platz 2016 ²⁹	L	L	L	L	L	L
Villanueva 2016 ³⁰	L	L	M	L	H	L
Coiro 2016 ³¹	L	M	L	L	L	L
Miglioranza 2017 ³²	L	L	L	L	L	L
Pellicori 2018 ³³	L	L	L	L	L	L

L: low; M: moderate; H: high

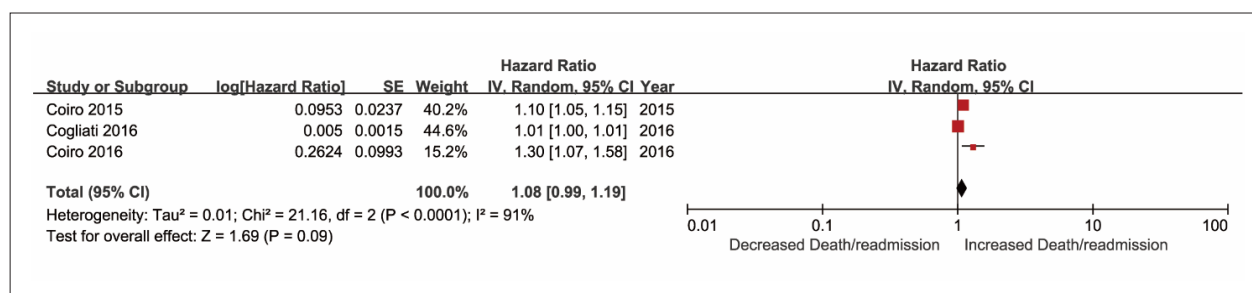


Figure 2 – Forest plots for discharge B-lines and combined outcomes of all-cause mortality or HF hospitalization.

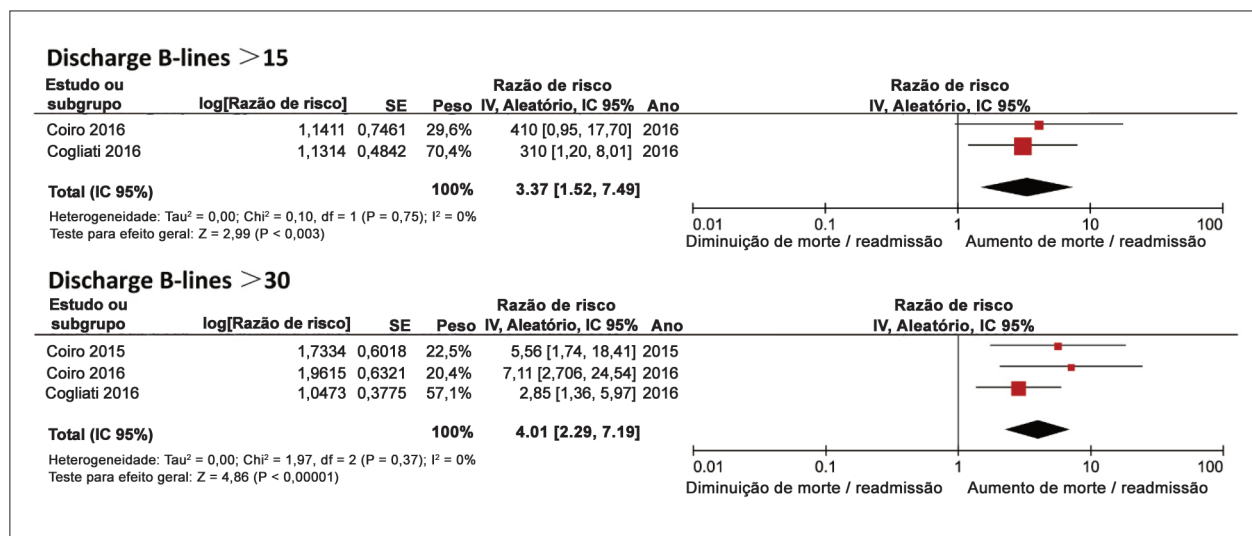


Figure 3 – Subgroup analysis of discharge B-lines and combined outcomes of all-cause mortality or HF hospitalization.

Discussion

The present meta-analysis indicated that, in patients with HF, B-lines >15 and >30 cutoff at discharge were predictive of the composite outcome of all-cause mortality or HF readmission in hospitalized patients. Additionally, a B-line >30 cutoff

at discharge was predictive of HF hospitalization. In HF outpatients, B-lines >3 strongly predicted the composite outcomes of all-cause mortality or HF readmission. Given the heterogeneity across the included studies and limited sample size, these findings should be considered as hypothesis-generating for future research.

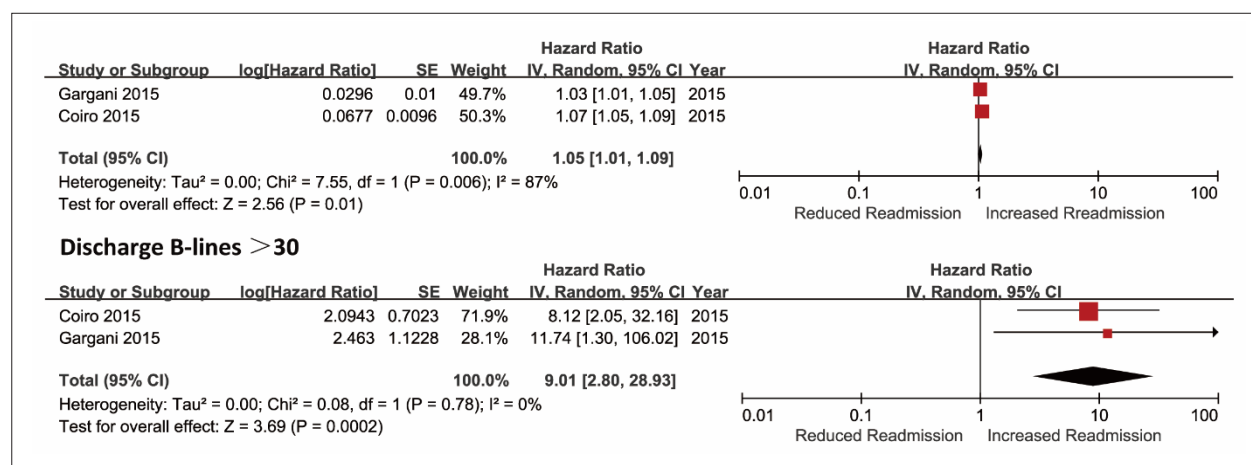


Figure 4 – Forest plots for B-lines and HF hospitalization.

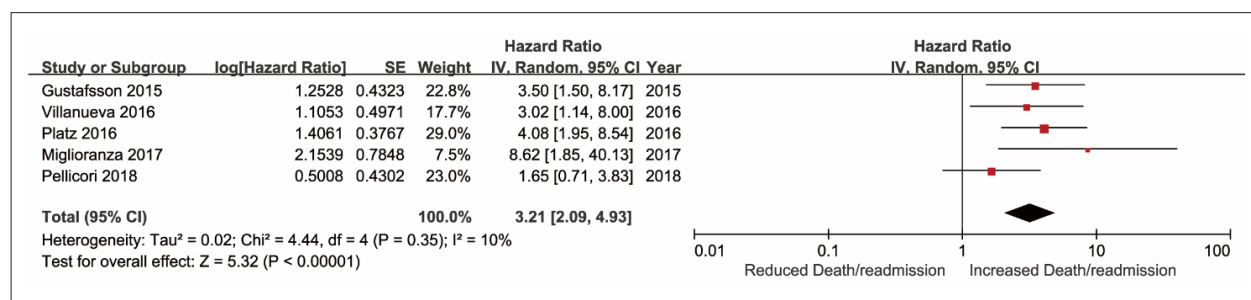


Figure 5 – Forest plots for B-lines and combined outcomes of all-cause mortality or HF hospitalization in HF outpatients.

A recent systematic review suggested that plenty of B-lines in patients with decompensated HF identified that those were at high level of risk for adverse events.³⁴ However, this review consisted of only five studies evaluating the prognostic value of LUS in HF and did not perform meta-analysis based on different numbers of B-lines at discharge. Another review supported the use of LUS in the management of acute decompensated HF, both as a diagnostic modality and in monitoring HF therapy.³⁵ In a moderate to severe systolic HF outpatient clinic, a study demonstrated that B-lines were significantly associated with more clinically established parameters of decompensation, such as the amino-terminal portion of B-type natriuretic peptide (NT-proBNP), clinical congestion score and E/e' ratio, and B-line ≥ 15 cutoff suggested HF decompensation.³⁶ However, the prognostic value of B-lines that is incremental to risk factors as well as those established indicators of clinical congestion in HF patients require further investigation.

There is a paucity of data describing features of B-lines and their differences in HF patients with preserved (HFpEF) and reduced (HFrEF) ventricular systolic function. The included studies enrolled HF patients but demonstrated their results without stratification by EF. Although congestion improves substantially during hospitalization in response to standard therapy alone, patients with HFrEF and with absent or minimal resting signs and symptoms at discharge evaluated by BNP and clinical congestion score still experienced high mortality

and readmission rates.³⁷ Importantly, the study by Coiro et al. demonstrated that the addition of ≥ 15 and ≥ 30 B-lines to BNP and the New York Heart Association (NYHA) class had improved risk classification, and B-lines independently predicted mortality and hospitalization for HF.²⁶ The absence or a small amount of B-lines identified those at extremely low risk of HF rehospitalization, but whether dealing with this residual pulmonary congestion would improve patient outcome should be the issue of further investigation.³⁸

The gold standard has not yet been established for the quantitative assessment of pulmonary congestion. Of note, patient positioning may affect the number of B-lines in HF patients, for example, the number of B-lines was lower in the sitting than in the supine position.³⁹ Moreover, two studies^{25,27} included in this review and meta-analysis used both methods of the 28 and 8 scanning regions for LUS examinations. These two methods have been recommended as useful in the assessment of pulmonary edema.⁴⁰ Nevertheless, in the reporting LUS findings, it will be important that both continuous and categorical data are standardized to present LUS measures (e.g. number of lung regions) to facilitate comparison of results across HF studies. The included studies in the present work indicated the prognostic value of B-lines in both in- and outpatients with HF. However, as they had different outcomes of interest (hospitalization due to HF versus composite outcomes of hospitalization and mortality)

and different clinical follow-up periods (3 *versus* 6 months), there is a slight difference in the reported optimal cut-off point for B-lines, however, they ranged between 15 and 30. Large randomized controlled trials are required to investigate to what extent the use of LUS would benefit HF patients. Moreover, more studies are needed to find out whether LUS could be applied to identify different phenotypes of patients with HF and to be tailored to the individual patient's needs.

Limitations

By design, our analysis did not allow the demonstration of the superiority of B-lines compared to other established biomarkers of HF, such as the NYHA class, NT-proBNP, or 6-min walk test, nor did we evaluate the incremental prognostic value of B-lines over established markers for congestion. Moreover, to our best knowledge, although we are providing the first review and meta-analysis of B-lines in patients with HF, further studies are needed for the optimal treatment of patients with HF with regard to the integrative value of B-lines associated with BNP or risk factors. Thirdly, substantial heterogeneity in this review and meta-analysis among studies indeed existed. The included articles with different patients' characteristics, B-lines quantification, and risk of bias may contribute to heterogeneity across studies. Also, the number of patients included in our meta-analysis was relatively small, which may have an impact on the exact quantification of the prognostic value of B-lines. In addition, the included studies considered different outcomes. Only one study²⁴ provided B-lines values both at admission and discharge for combined outcomes of all-cause mortality or HF hospitalization. It would be interesting to examine the changes between the numbers or positions of B-lines at admission and before discharge.

Conclusions

The present meta-analysis demonstrated that the B-lines could predict all-cause mortality and HF hospitalizations in patients with HF. Further large randomized controlled trials are needed to explore whether dealing with B-lines would improve the prognosis in clinical settings.

Author contributions

Conception and design of the research and Acquisition of data: Wang Y, Ma M; Analysis and interpretation of the data and Statistical analysis: Shi D, Liu F; Obtaining financing: Wang Y, Xu P; Writing of the manuscript: Wang Y, Shi D, Ma M; Critical revision of the manuscript for intellectual content: Xu P, Ma M.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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*Supplemental Materials

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Is There a Role for Lung Ultrasonography in the Prognosis of Heart Failure Patients?

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Short Editorial related to the article: Prognostic Value of Lung Ultrasound for Clinical Outcomes in Heart Failure Patients: A Systematic Review and Meta-Analysis

Heart failure (HF) hospitalizations are most commonly motivated by systemic and pulmonary congestion, leading to 5–15% of mortality rate and up to 50% of readmission rate in 90 days.¹ Although the usual goal during hospitalization is complete decongestion, 30% of patients have residual congestion at discharge.² Signs of congestion, high filling pressures and elevated natriuretic peptides are associated with higher mortality and readmission rates, and residual congestion at discharge is also associated with worse prognosis.^{3,4}

Congestion assessment is usually difficult given the low sensitivity and/or specificity of physical examination findings.¹ Chest radiography and natriuretic peptides can improve evaluation, but lung ultrasonography (LUS) has been recently used as a sensitive tool in this scenario.⁵ It can estimate right atrial pressure using vena cava diameter and variation and evaluate lung congestion by counting B-lines in chest zones. B-lines are hyperechoic artefacts on LUS which appear as vertical lines from the pleural line to the bottom of the screen and represent thickening of interlobular septa. Recent data report association of B-lines in LUS with higher mortality and hospitalization rates.⁶

In this issue of *Arquivos Brasileiros de Cardiologia*, a systematic review and metanalysis evaluated the prognostic value of pulmonary congestion represented by B-lines in patients with HF.⁷ The metanalysis included 8 studies involving hospitalized and outpatients and three different analyses were executed. Firstly, among hospitalized HF patients, >15 and >30 B-lines at discharge significantly correlated with increased risk of death or HF hospitalization in three studies (HR, 3.37, 95% CI, 1.52–7.47; $I^2=0\%$ $p=0.003$ and HR, 4.01, 95% IC 2.29–7.01; $I^2=0\%$, $p<0.001$, respectively). Secondly,

B-lines at discharge were associated with increased risk of hospitalization in two other studies (HR, 1.05, 95% CI 1.01–1.09, $I^2=87\%$, $p=0.01$), with higher association and lower heterogeneity in subgroup analysis considering B-lines>30 at discharge (HR, 9.01, 95% CI, 2.08–28.93, $I^2=0\%$, $p<0.001$). Thirdly, among outpatients, B-lines>3 significantly increased risk of death or HF hospitalization in five studies (HR, 3.21, 95% IC, 2.09–4.93, $I^2=10\%$, $p<0.00001$).

Some limitations must be highlighted: the heterogeneity of studies did not allow the authors to define a single primary outcome to include all studies, thus limiting the number of patients for each analysis. There are different protocols for B-line evaluation, and management of HF patients was not evaluated. None of the studies stratified HF by ejection fraction, although the mean ejection fraction of all studies was below 50%. Large randomized trials are required to confirm these findings.

On the other hand, this metanalysis enables us to formulate a hypothesis. Congestion evaluation at discharge is often flawed, but, at the same time, decongestion is fundamental.⁸ Therefore, an extra tool could be used to help achieving decongestion. This was the rationale for the PRIMA II trial, a randomized trial evaluating N-terminal pro-B-type natriuretic peptide as a target to discharge acute decompensated HF patients, but no difference was found in death or hospitalizations in 180 days.⁹ But what would be the effects of LUS evaluation at discharge targeting a certain number of B-lines? Would it help guiding therapy towards complete decongestion? Ultimately, would it reduce hospitalizations and mortality in HF? Definitely, more data is needed, and this is a promising field.

Keywords

Heart Failure; Prognosis; Hospitalization; Mortality; Lung/ultrasonography; Natriuretic Peptides.

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Mortal Interaction Between Hemophagocytic Syndrome and Newly Developed Heart Failure

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Abstract

Background: Hemophagocytic syndrome (HPS) is a devastating hyperinflammatory syndrome. Heart failure (HF) with preserved ejection fraction (HFpEF) status is closely correlated with increased inflammation, both systemic and intramyocardial.

Objectives: This study sought to determine mortality predictors and reliable follow-up parameters in HPS that developed HFpEF during the clinical course.

Methods: Thirty-nine patients, diagnosed as HPS, according to HLH 2004 diagnostic criteria, with an HScore of ≥ 169 and proven bone marrow aspiration or biopsy, were recruited retrospectively. Both traditional, serum C-reactive protein, albumin and ferritin levels with lymphocyte, and platelet counts, as well as non-traditional risk factors, neutrophil-to-lymphocyte count (NLR), monocyte-to-lymphocyte count (MLR), mean platelet volume (MPV), and N-Terminal pro-brain natriuretic peptide (NTproBNP), were investigated retrospectively. The relationship between time-changed laboratory values both among themselves and with mortality. The overall significance level was set at 5%.

Results: This study showed that temporal change of cardiothoracic ratio (CTR), serum NTproBNP, ferritin, CRP, and albumin levels were detected as mortality predictors ($p < 0.05$, for all) in the univariate analysis. Lymphocyte and platelet counts with NLR and MPV values were also significant ($p < 0.05$). The relationship between NT-proBNP and increased systemic inflammatory markers proved to be significant. In addition to traditional risk factors, serum ferritin levels, NLR, MLR, and MPV levels also proved to be significantly correlated with each other.

Conclusion: Accompanied by reliable follow-up parameters, rapid diagnosis and aggressive anti-inflammatory treatment with tight volume control can be life-saving in HPS patients who suffer from HFpEF. Close monitoring of inflammation may predict the outcome of patients suffering from HFpEF. (Arq Bras Cardiol. 2021; 116(3):395-401)

Keywords: Heart failure; Hemaphogocytic Lymphohistiocytosis, Inflammation, Mortality.

Introduction

Hemophagocytic syndrome (HPS) is a devastating prototype of severe systemic hyperinflammation. HPS is a clinical syndrome that is frequently lethal due to organ and tissue invasion of increased T lymphocytes with excess cytokine by continuous inflammation in individuals with pathogen clearance disorder. Patient diagnoses may be confused with sepsis due to its non-specific findings, including fever, hepatosplenomegaly, lymphadenomegaly, elevated liver enzymes, and cytopenias. Mortality rates are high

both due to this and delayed diagnosis.¹ In this syndrome, which is characterized by an excessive cytokine storm, many organs can be irreversibly damaged and death is inevitable in the absence of immediate anti-inflammatory and/or anti-cytokine treatment. The heart, undoubtedly affected by increased inflammation, is the organ most closely associated with the immune system within all organ systems. The relationship between myocardial suppression and increased inflammation is a well-known fact. Another prototype of increased inflammation studies in individuals with sepsis has shown that the majority of patients have a more heart failure (HF) with preserved ejection fraction (HFpEF) clinical picture in the early stages.

As a result, the signs and symptoms of patients with HPS is various and might refer to the hospital with decompensated heart failure. HFpEF, nearly half of the patients' hospitalization due to heart failure, is diagnosed based on the signs and symptoms of heart failure, normal or only mild abnormal left ventricular systolic function (left ventricular ejection fraction

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>50%), and evidence of diastolic dysfunction. Elevated ventricular filling pressures are the prominent hemodynamic abnormality in both chronic and acute heart failure. Many previous studies have shown high levels of pro-inflammatory status in the peripheral circulation and heart of HF patients. Moreover, these studies emphasized that the existence of a repetitive and progressive state of immuno-inflammatory activation is strongly associated with the progression of ventricular diastolic dysfunction and HFpEF.²⁻⁹

If we accept HPS as the prototype of severe systemic inflammation, it is not surprising that HFpEF develops in the course of HPS. Information is still scarce in the literature on the most effective proven treatment for HFpEF patients other than supportive measures, including lifestyle modification, hypertension management, metabolic control for diabetes, and obesity. More recently, the protein kinase G pathway stimulation seems to open the horizon in the future. After it became clear that HPS patients were complicated by heart failure, it was important to investigate the presence of possible reversal parameters or any predictors in these patients that had been followed up on in the past. This study hypothesized that inflammation is the main source for myocardial depression, and the hyperinflammatory state were stopped, myocardial dysintegrity could be reversed.⁹ In this light, this study aimed to determine mortality predictors and reliable follow-up parameters in HPS that developed HFpEF during the clinical course.

Material Method

Patients

Data from patients (n=63) who were hospitalized due to the HPS, according to the HLH 2004 diagnostic criteria between January 2012 and December 2018, were collected retrospectively.^{10,11} HPS patients with proven bone marrow aspiration or biopsy, with detailed echocardiography reports, over 18 years of age, and hospitalized more than three days, with hemophagocytosis score (HScore)⁶ of 169 and above were included in the study. The HFpEF group was defined according to the 2016 ESC Guideline.¹⁰ Detailed medical history for each patient, including the first clinical and laboratory findings referring to HPS, were recorded retrospectively. Finally, 39 patients, who presented available blood biochemistry results and newly developed heart failure symptoms during hospitalization, were included in the study. Patient who had been hospitalized ≤ 3 days, presenting malignancy or a previous history of chemotherapy and no sufficient data,, including available electrocardiographic reports and HPS diagnostic laboratory values, were excluded from the study.

Data sources

Patients' data were evaluated retrospectively by four specialist physicians, including an expert cardiologist, hematologist, rheumatologist, and intensive care physician. Clinical characteristics, medical history, and laboratory parameters were recorded from patients' medical files and the hospital's digital data system retrospectively. The time

(T-to-t, in days) between the first symptom or laboratory data suggestive of HPS and the beginning of effective treatment was also determined. At the time of diagnosis, the HScore was calculated according to findings from Fardet et al.⁶ Complete blood count reports, including polymorphous nucleated leucocyte count (PMNL), monocyte count, lymphocyte count (L), platelet count (PLT), and mean platelet volume (MPV) were recorded. All N terminal-pro brain natriuretic peptide (NTproBNP) levels during hospitalization were also recorded. NLR was obtained by dividing the venous absolute circulating neutrophil count by the lymphocyte count. MLR was obtained by dividing the monocyte count by the lymphocyte count. Transthoracic echocardiographic examination reports, performed by an experienced cardiologist, as recommended by the American Society of Echocardiography,¹² were collected retrospectively. Likewise, the cardiothoracic ratio (CTR) for patients suffering from heart failure was also calculated according to previously recorded chest radiographies.¹³ The CTR was calculated by dividing the maximal horizontal width of the heart by the horizontal diameter of the inner borders of the rib cage. Analysis was performed by the same operational team, using computer software to ensure measurement accuracy. The two laboratory values of the patients at the time of hospitalization (baseline, B) and at the end of hospitalization (final, F), either dead or discharged, were examined. Temporal changes of all values during the hospital course were represented as 'Δ'.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the medical ethics committee at the Hospital of the Faculty of Medicine, Ege University, Izmir, Turkey.

Statistical analysis

The compatibility of continuous variables to normal distribution was checked separately in each group by the Shapiro-Wilk test. Categorical variables were determined as a summarized count, in a percentage form, whereas continuous variables were determined as a summarized median, an interquartile range (IQR). Non-parametric methods were preferred, as the majority of numerical variables failed to provide normal distribution (Mann Whitney U test and Spearman's correlation analysis). Categorical variables were analyzed by the Chi-Square test and numerical variables were analyzed by the Mann-Whitney U Test. The differences between mortality and non-mortality groups were evaluated by the Mann Whitney U test. Spearman's correlation analysis was performed between the mortality parameters. The overall significance level was set at 5%. The IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 25 (IBM Corp., Armonk, NY, USA), was used for analysis.

Results

In total, 39 patients (n=25, 64.1% female), median of 45.0 (22.0) years of age, were included in this study. Of these, 10 (25.6%) patients died (mortality group), and 29 were discharged from the hospital (survival group). Baseline clinical characteristics and laboratory parameters of the two groups are summarized in Table 1. No significant difference

Table 1 – Comparison of baseline characteristics and laboratory parameters

Variable	Mortality group Median (IQR) (n=10)	Survival group Median (IQR) (n=29)	p
Age, year	47.0 (29.0)	44.5 (22.0)	0.764
Sex, female %	60 (n=6)	63.3 (19)	0.855
Systolic blood pressure	96.5 (27.0)	96.5 (21)	0.464
Diastolic blood pressure	59.0 (17.0)	60.0 (15.0)	0.173
Hscore	223 (100)	229.0(39.0)	0.868
Hospitalization length, day	10.0 (6.0)	15.0 (15.0)	0.379
NT-proBNP(ng/L)	2390 (69930)	4000(69960)	0.746
Ferritin (mcg/L)	4303 (169700)	21110 (98300)	0.216
Fibrinogen (mg/mL)	257 (171)	318 (272)	0.289
Sedimentation (hours)	65.0 (46.0)	66.0 (41.0)	0.553
INR	1.1 (1.9)	1.1 (1.2)	0.161
Albumine (mg/dL)	2.9 (3.0)	3.0 (2.4)	0.842
Globuline (mg/dL)	2.6 (0.8)	3.3 (1.0)	0.088
Urea (mg/dL)	44.0 (122)	349.0 (268)	0.128
Creatinine (mg/dL)	0.73 (6.04)	0.8 (11.11)	0.202
LDH	583.0 (8840)	404.0 (5540)	0.197
CRP	6.32 (34.26)	8.4 (36.54)	0.406
Hemoglobin (g/dL)	9.7 (11.1)	8.7 (6.9)	0.204
Platelet X 10 ³	66 (442.0)	115.5 (749.0)	0.479
Neutrophil	3500.0 (27200)	5800.0 (7800.0)	0.606

Mann Whitney U test for continuous variables, Chi-square test for categorical variables. CRP: c-reactive protein, IQR: interquartile range, LDH: lactate dehydrogenase, NTproBNP: N-terminal pro-B-type natriuretic peptide.

was observed among the groups in terms of laboratory parameters. No medical histories of patients were found, except for two patients with hypertension in the survival group. The underlying etiologies were: infectious disease (n=10), rheumatological diseases (n=20), malignancy (n=3), and idiopathic origin (n=6). Four patients who presented infectious etiology, 2 with rheumatological disease, 3 with malignancy, and 1 of idiopathic origin died. During the hospitalization period, seven patients underwent hemodialysis, primarily to achieve adequate ultrafiltration, while 25 patients received loop-diuretic infusion due to the hypervolemia.

There was no significant difference in the net ultrafiltration liters between the mortality group and the survival group (11.5 (3.8) and 10.5 (6.0), $p=0.408$, respectively). Final laboratory values of alive and deceased patients with the entire study population were presented in Table 2. The mean time spent from the first symptoms to the beginning of adequate anti-inflammatory treatment (T-to-t), CTR, NT-ProBNP, CRP, ferritin, LDH, MLR and final MPV were significantly higher in the mortality group than in the survival group. Moreover, the mean albumine, lymphocyte, and platelet counts were statistically much lower in the mortality group than in the survival group. During the ICU stay, the temporal change of CTR, serum NTproBNP, ferritin, CRP, and albumin levels were detected as mortality predictors ($p<0.05$, for all). Lymphocyte and

platelet counts with NLR and MPV values were also significant ($p<0.05$, for all) (Table 3). Temporal changes in the MLR value failed to achieve the statistical significance ($p=0.052$). Spearman's correlation analysis showed the significant correlations between the traditional and non-traditional risk parameters with the temporal changes (Table-4). This study schematized the lethal interaction between HPS and HFpEF via laboratory markers and the cardiorenal axis in Figure 1.

Discussion

The present study showed that the temporal changes of traditional (serum CRP, albumin, and ferritin levels with lymphocyte and platelet counts), and non-traditional (NLR, MPV, NTpBNP, and CTR counts) laboratory markers of increased inflammation are significantly associated with the mortality of patients with HSP during follow-up. The relationship between NT-proBNP and increased systemic inflammation markers proved to be significant.¹⁴ In addition to traditional risk factors, temporal changes of serum ferritin levels, NLR, MLR, and MPV levels proved to be significantly correlated with each other.¹⁵⁻¹⁷

The fact that the platelet count, which is a positive acute phase reactant, appears to be a negative acute phase reactant in this study, is related to the discontinuation of

Table 2 – Final laboratory values of deceased and living patients during hospital stay

Variable	Mortality group (n=10) Median (IQR)	Survival group (n=29) Median (IQR)	p
T-to-t (in days)	24.0 (60.0)	10.0 (28.8)	0.001
CTR (%)	56.0 (37.0)	50.0 (56.71)	0.026
NTproBNP (x10 ³ ng/L)	2.7 (70.0)	1.1 (25.7)	0.023
Albumin (g/dL)	2.7 (2.5)	3.3(2.1)	0.035
CRP (mg/dL)	7.9 (41.7)	1.4 (19.0)	0.005
Ferritin (x10 ³ mcg/L)	2.58 (120.0)	0.64 (1.53)	0.047
LDH (x10 ³ U/L)	0.56 (5.9)	0.2 (0.8)	<0.001
L (x10 ³ /μL)	0.77 (9.4)	1.5 (4.2)	0.010
PLT (x10 ³ /μL)	47.0 (418.0)	188.5 (546.0)	<0.001
NLR	7.6 (52.2)	2.79 (14.4)	<0.001
MPV	Baseline	11.7 (7.1)	0.035
	Final	11.8 (9.1)	0.027
MLR	1.0 (1.0)	0.5 (0.2)	<0.001

CRP: C-reactive protein; CTR: Cardiothoracic ratio; IQR: interquartile range; NLR: Neutrophil-to-lymphocyte ratio; L: Lymphocyte count; LDH: Lactate dehydrogenase; MPV: Mean platelet volume; MLR: Monocyte-to-lymphocyte ratio; NTproBNP: N-terminal pro-B-type natriuretic peptide; PLT: Platelet count; T-to-t (in days): Time spent to begin treatment. For continuous variables, the Mann Whitney U test was performed.

Table 3 – Temporal change of mortality predictors

Parameters	Survival group (n=29)	Mortality group (n=10)	p
	Median (IQR)	Median (IQR)	
ΔNTproBNP(x10 ³ ng/L)	-4.67(12.35)	28.26(49.91)	0.007
Δ CTR (%)	-10.1(4.00)	4.0(10.00)	0.001
Δ Ferritin(x10 ³ mcg/L)	-3.42(18.08)	42.11(179.83)	0.020
Δ LDH (x10 ³ U/L)	-0.31(0.43)	-2.0(3.68)	0.571
Δ CRP (mg/dL)	-6.8(16.98)	0.0(11.15)	0.001
Δ Albumin (g/dL)	0.40(0.95)	-0.35(0.75)	0.026
Δ L(x10 ³ /μL)	0.53(0.75)	-0.85(660)	0.001
Δ PLT(x10 ³ /μL)	68.05 (119.00)	-29.5 (56.25)	0.001
Δ NLR	-2.77(8.37)	4.6(12.09)	0.001
Δ MPV	-1.2(1.92)	0.85(1.8)	0.040
Δ MLR	-0.11(0.57)	0.34(1.61)	0.052

Δ' (Delta) refers to the change of any laboratory parameter value during hospital stay. It is calculated as the final value, either discharged or deceased, minus the baseline value, which is the first biochemical laboratory data. CRP: C-reactive protein; CTR: Cardiothoracic ratio; IQR: interquartile range; NLR: Neutrophil-to-lymphocyte ratio; L: Lymphocyte count; LDH: Lactate dehydrogenase; MPV: Mean platelet volume; MLR: Monocyte-to-lymphocyte ratio; NTproBNP: N-terminal pro-B-type natriuretic peptide; PLT: Platelet count. For continuous variables, the Mann Whitney U test was performed.

platelet consumption in the case of possibly controlled hemophagocytosis. The relationship between the lymphocyte count and well-being, which has been shown in many clinical inflammatory conditions, was also confirmed in this study.^{18,19} These are the first screening parameters for patients with HFpEF. The main reason for mortality in patients with HFpEF is due to non-cardiac reasons.^{20,21} To date, the guidelines offer no treatment other than the treatment with diuretics or the

treatment focusing on underlying causes.^{9,21} It was recently shown that the N-terminal pro-B-type natriuretic peptide (NT-proBNP) may have some advantages.^{10,22} NT-proBNP is a well-established tool to predict patient mortality in both heart failure with reduced or preserved ejection fraction. However, there is little data on the relationship between this parameter and patient survival during hospitalization. The present study showed that temporal changes of NT-proBNP are closely

Original Article

Table 4 – Spearman's correlation analysis between risk parameters

	CC (R ²)	p		CC (R ²)	p
Δ NTproBNP			Δ CTR		
Δ CTR	0.432	0.095	Δ NLR	0.461	0.031
Δ Ferritin	0.587	0.027	Δ MPV	0.561	0.004
Δ Albumin	-0.520	0.022	Δ MLR	0.404	0.041
Δ CRP	0.498	0.039	Δ PLT	-0.651	0.001
Δ PLT	-0.488	0.047	Δ CRP	0.411	0.041
Δ NLR	0.705	0.001	Δ NLR		
Δ MLR	0.478	0.038	Δ CRP	0.597	0.001
Δ Albumin			Δ Ferritin	0.592	0.002
Δ NLR	-0.417	0.013	Δ PLT	-0.601	0.002
Δ MPV	-0.334	0.046	Δ L		
Δ Ferritin	-0.397	0.049	Δ Ferritin	-0.507	0.010
Δ PLT	0.341	0.039	Δ CRP	-0.531	0.001

Delta (Δ) reflects the temporal change of any parameter during hospital stay. CRP: C-reactive protein; CTR: Cardiothoracic ratio; NLR: Neutrophil-to-lymphocyte ratio; L: Lymphocyte count; LDH: Lactate dehydrogenase; MPV: Mean platelet volume; MLR: Monocyte-to-lymphocyte ratio; NTproBNP: N-terminal pro-B-type natriuretic peptide; PLT: Platelet count.

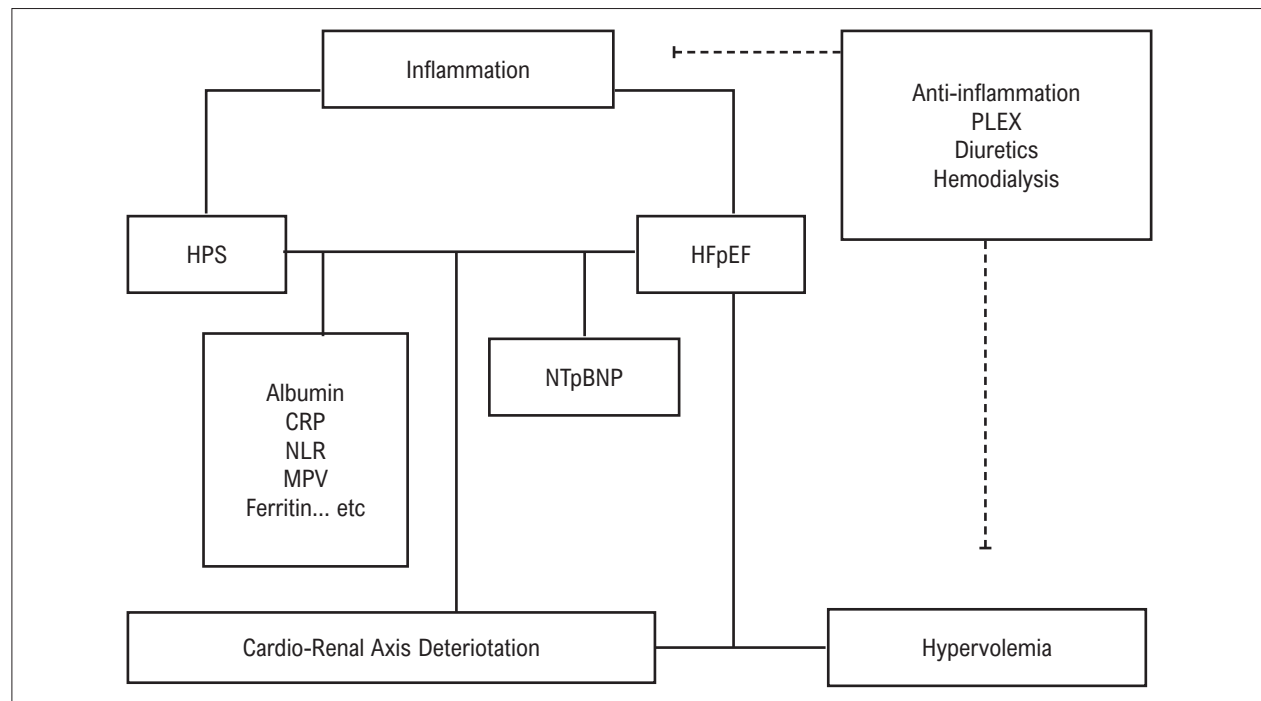


Figure 1 - A crisscross between HPS and HFpEF. HPS, hemophagocytic syndrome; NTproBNP: N-Terminal pro brain natriuretic peptide; CRP: C-reactive protein; NLR: Neutrophil-to-lymphocyte count; MPV: mean platelet volume; HFpEF: heart failure with preserved ejection fraction; PLEX: plasmapheresis.

associated with patient mortality. The main goal of HPS-related HFpEF is to stop the presence of increased proinflammatory status as soon as possible; otherwise, death is inevitable. Time spent from the onset of first symptoms to the beginning of treatment directly affects patient survival, as shown above. Since rapid and effective treatment has been implemented, a lower mortality rate has been achieved, when compared to

the literature.²² In our population, the overall mortality rate is 25.6% and the malignancy censored mortality rate is 19.4%. Cardiorenal axis deterioration is another important scene in HFpEF patients.²³ Due to the high ventricular filling pressures, most patients present high central venous and intra abdominal pressure. Increased renin angiotensin system activation and reduced renal plasma flow may worsen renal functions. In

addition, inappropriate volume loading leads to increased preloading, with an increase in failure symptoms, coupled with worsening renal functions. Positive fluid balance during diastolic dysfunction closely associated with mortality has been also shown.^{24,25} Strict volume control with continuous diuretic infusion and ultrafiltration procedures, as well as improvements in renal function tests, which provided survival benefits, were also achieved. This reflects the recovery of acute kidney injury. However, no changes reached statistical significance. The small number of study patients may play a role in this. With an early and effective control of inflammation and hypervolemia, it is certain that survival will increase in this population.

Limitation

There are some limitations to this study, one of which is the retrospective design. The risk of bias in the study cannot be ignored. However, the data were collected by four researchers who are experts in their respective fields. The etiology of heterogeneous disease may have a different risk of mortality. However, we believe that this is a very important study to determine the risk of heart failure in the course of HPS and to identify the markers that will affect survival in patient follow-up. Even if there were no genetic tests, cytokine level measurements, and no specific laboratory measurement results, the patients were selected meticulously, according to the 2004 HLH study criteria and hemophagocytosis scoring results.^{11,26} It should be noted that, due to the different etiologies of HPS (including systemic lupus erythematosus, the onset of Adult Still's disease, rheumatoid arthritis, mixed connective tissue disease, and infectious causes), this study faced an inevitable heterogeneity.

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Conclusion

The present study illustrated that simple and cheap blood parameters, which can be easily obtained, may be an early warning for physicians during routine follow-up of HPS patients suffering from HFpEF. Our non-traditional follow-up parameters are valuable in HPS complicated with HFpEF, which is generally difficult to manage and leads to high mortality rates. This study also proposes the interruption of inflammation as soon as possible in order to protect the heart.

Author contributions

Conception and design of the research: Bozkurt D; Data acquisition: Bozgul SMK, Emgin O, Butun O, Simsek E, Hekimgil M; Analysis and interpretation of the data: Emgin O, Butun O, Hekimgil M; Statistical analysis: Kose T; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Bozkurt D, Kilic S.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Hyperinflammatory Syndrome as a Cardiac Injury Mechanism

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Short Editorial related to the article: Mortal Interaction Between Hemophagocytic Syndrome and Newly Developed Heart Failure

Hemophagocytic syndrome (HPS) or hemophagocytic lymphohistiocytosis (HLH) is an acute and rapidly progressive systemic inflammatory disorder characterized by cytopenia, excessive cytokine production and hyperferritinemia. Common clinical manifestations of HLH are acute unremitting fever, lymphadenopathy, hepatosplenomegaly and multiple-organ failure. It consists of two different conditions that may be difficult to distinguish: a primary form is mostly seen in children and is caused by various mutations with genetic inheritance and a secondary HLH may be secondary to a malignant, infectious, or autoimmune/autoinflammatory stimulus without an identifiable underlying genetic trigger.^{1,2}

The hyperinflammatory immune state is caused by the absence of normal downregulation by activated macrophages and lymphocytes. Most patients with HLH have impaired cytotoxic function of natural killer (NK) cells and cytotoxic lymphocytes (CTLs), coupled with excessive activation of macrophages.³ Lack of feedback regulation results in excessive macrophage activity and high levels of interferon gamma and other cytokines. Excessive cytokine production by macrophages, NK cells, and CTLs is a primary mediator of tissue damage.⁴

HLH may be suspected in infants, children or adults with unknown cytopenia, hepatitis or inflammatory central nervous system findings. Patients present unknown fever, hepatosplenomegaly, prior HLH-like episodes, family history of HLH or a known genetic disorder associated with HLH.⁵ The outcome of untreated HLH syndrome is often fatal. Clinical complexity, rarity, and diversity of causes require the physicians pay a great deal of attention to this diagnostic possibility. Prompt recognition of the HLH syndrome and diagnosis of the underlying causes of HLH is vital to enable urgent and appropriate treatment.²

In this edition of Arquivos Brasileiros de Cardiologia, the authors evaluated retrospective data of 39 patients with

secondary HLH diagnosis according to HLH 2004 diagnostic criteria.⁶ They showed that non-traditional laboratory markers of increased inflammation are significantly associated with patient mortality during follow-up. Among the markers, both the N-terminal prohormone of brain natriuretic peptide (NT-proBNP) final value and laboratory parameter variation values during hospital stay presented a higher mortality rate. This marker is useful to predict mortality regarding heart failure both with preserved and reduced ejection fraction. Therefore, this study shows the relationship between NT-proBNP and patient survival during hospitalization.⁶

NT-proBNP is associated with myocardial damage, stress, fibrosis and systemic inflammation, and high NT-proBNP levels constitute an independent diagnostic criterion for heart failure with preserved ejection fraction.^{7,8} It is known that inflammatory states may trigger cardiac injury such as heart failure, which was described in COVID-19 diseases as well as others with high inflammation rate.⁹ However, it is important to understand that a moderately high NT-proBNP level in a patient with inflammation must be interpreted with caution: such inflammatory state may increase NT-proBNP/BNP ratio and overestimate HF severity. Inflammation may increase protease or receptor-mediated clearance of BNP and NT-proBNP, which is not affected by these clearance mechanisms, resulting in an increased NT-proBNP/BNP ratio.¹⁰

In conditions other than HLH, high NT-proBNP levels are correlated with unfavorable outcomes. A systematic review of 46 studies of septic shock concluded that high levels of BNP and NT-proBNP were associated with increased mortality regardless of cardiac dysfunction. Furthermore, this marker may be used to distinguish between septic and cardiogenic shock.¹¹ In another study with patients diagnosed with multiple myeloma (MM), NT-proBNP levels rose significantly such as other disease severity markers. MM may cause cardiac injury such as cardiac amyloidosis, but, in some cases, NT-proBNP suggests inflammation as the link between MM and functional cardiac impairment.¹²

As presented in this editorial, NT-proBNP is a marker of cardiac dysfunction, but it is also associated with severe inflammatory conditions. This correlation can help physicians identify high inflammatory states in order to introduce prompt treatment. Furthermore, if the patient presents cardiac dysfunction, the marker plays an important role in find out such condition. This makes it possible to prevent harm against the heart such as hypervolemia or the use of cardiac depressants drugs.⁶

Keywords

Hemophagocytic; Heart Failure; NT-proBNP; Hyperinflammation.

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Histopathological Characterization of Mitral Valvular Lesions from Patients with Rheumatic Heart Disease

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Abstract

Background: The underlying mechanisms by which rheumatic heart disease (RHD) lead to severe valve dysfunction are not completely understood.

Objective: The present study evaluated the histopathological changes in mitral valves (MV) seeking an association between the pattern of predominant valvular dysfunction and histopathological findings.

Methods: In 40 patients who underwent MV replacement due to RHD, and in 20 controls that underwent heart transplant, histological aspects of the excised MV were analyzed. Clinical and echocardiographic data were also collected. Histological analyses were performed using hematoxylin-eosin staining. Inflammation, fibrosis, neoangiogenesis, calcification and adipose metaplasia were determined. A p value < 0.05 was considered to be statistically significant.

Results: The mean age of RHD patients was 53 ± 13 years, 36 (90%) were female, whereas the mean age of controls was 50 ± 12 years, similar to the cases, with the majority of males (70%). The rheumatic valve endocardium presented greater thickness than the controls (1.3 ± 0.5 mm versus 0.90 ± 0.4 mm, $p = 0.003$, respectively), and a more intense inflammatory infiltrate in the endocardium (78% versus 36%; $p = 0.004$), with predominance of mononuclear cells. Moderate to marked fibrosis occurred more frequently in rheumatic valves than in control valves (100% vs. 29%; $p < 0.001$). Calcification occurred in 35% of rheumatic valves, especially among stenotic valves, which was associated with the mitral valve area ($p = 0.003$).

Conclusions: Despite intense degree of fibrosis, the inflammatory process remains active in the rheumatic mitral valve, even at late disease with valve dysfunction. Calcification predominated in stenotic valves and in patients with right ventricular dysfunction. (Arq Bras Cardiol. 2021; 116(3):404-412)

Keywords: Rheumatic Disease; Calcification; Fibrosis; Inflammation; Rheumatic Fever; Myocarditis; Histology; Mitral Valve Stenosis; Echocardiography/methods.

Introduction

Rheumatic heart disease (RHD) remains a major public health concern, especially in low- and middle-income countries, where it is the leading cause of cardiovascular death in children and young adults.¹⁻³ It is estimated that 33 million individuals currently live with RHD, accounting for over a million premature deaths annually.¹ RHD has the highest cardiovascular disease-related loss of disability-adjusted-life-years (DALY) in children worldwide.⁴ Much of the morbidity and mortality of RHD can be prevented, but if left untreated,

subsequent heart failure and death are inevitable.^{5,6} Most deaths occur in young adults, who would otherwise be at the most productive years of their lives, indicating the devastating impact of this condition.^{6,7}

RHD is a harmful post-infectious sequel of acute rheumatic fever (ARF) resulting from an abnormal immune response to a streptococcal pharyngitis that triggers valvular damage.⁸ Unlike myocardium and pericardium, the valvular tissue often sustains permanent damage after active initial carditis.⁹ In the late stage of RHD, ongoing chronic inflammation continues leading to pathological valve remodeling that perpetuates valve damage over time.^{10,11} RHD most commonly and severely affects the mitral valve (MV) which, over time becomes dysfunctional, contributing to an increased risk of death and other major adverse outcomes.

Despite the observed progress in research on RHD pathogenesis, a number of key scientific questions remain.^{12,13} Specifically, the underlying mechanisms involved in the development of severe valve dysfunction are not completely understood.¹⁴ An active inflammatory process and endothelial

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activation are fundamental to perpetuate the progressive fibrotic leaflet remodeling and further valve dysfunction.¹⁵ Therefore, an improved understanding of this pathological process that leads to the development of severe valve dysfunction will provide insights into disease pathogenesis, and can ultimately lead to more effective therapeutic strategies to prevent irreversible valvular damage. In the present study, we hypothesized that the inflammatory process persists even in more advanced stages of the disease process, which contributes to progressive valve injury in RHD. The aim of this study is to evaluate the histopathological changes in mitral valves at an end stage of valve dysfunction, seeking an association between the pattern of predominant valvular dysfunction and histopathological findings.

Methods

Study population

A total of 60 mitral valves were collected from January 2015 to 2018, 40 were from RHD patients, and 20 were in the control group, which included all patients who underwent heart transplant due to severe heart failure, without primary valve lesion.

Patients referred to the University Hospital of Universidade Federal de Minas Gerais (HC-UFMG) diagnosed with rheumatic mitral valve disease, presenting stenosis or regurgitation, and with indication to mitral valve replacement surgery were eligible for the study.

The patients were informed about the study and invited to participate, voluntarily, during their follow-up before the surgical procedure. Treatment was offered to all patients, regardless of their willingness to participate in the study, and all those who agreed to participate signed an informed consent form. This study was approved by the Ethics Committee of Universidade Federal de Minas Gerais.

Clinical consultation, anamnesis and physical examination were performed to collect the clinical data prior to surgery, and the echocardiogram was performed at HC-UFMG Echocardiography Sector, for the collection of echocardiographic and imaging data.

Patient management and indication for mitral valve replacement was according to the recommended guidelines for valvular heart disease.^{16,17}

Surgeries were performed in the HC-UFMG Surgery Center and the valves were sent to the HC-UFMG Pathology Department for conventional histopathological examination, according to the routine established by the Cardiovascular and Cardiovascular Surgery Service of HC-UFMG, as well as the Laboratory of Molecular Pathology (LMP) of the Department of Pathological Anatomy and Legal Medicine of FM-UFMG, to carry out this study.

Echocardiographic evaluation

Two-dimensional (2D) echocardiography imaging and Doppler was performed using a commercially available system (Philips ie33, Andover, MA or GE Vivid-q Horten, Norway) in all patients. Standard echocardiograms were obtained

according to the American Society of Echocardiography guidelines.¹⁸ The conventional indexes for assessment of mitral stenosis severity, including mitral valve area, transmitral valve pressure gradients and pulmonary artery systolic pressure were measured, as recommended.

Histological analysis

The valves received in the LMP were examined and referred for histological processing according to routine laboratory protocols, including fixation, paraffin embedding, hematoxylin-eosin staining and microscopic analysis. Semi-quantitative analysis of the samples was carried out using a grade scale.

Parameters of inflammation intensity, identification of the predominant cell type and fibrosis intensity were evaluated, in addition to the presence of neoangiogenesis, calcification and adipose metaplasia.

Endocardial thickness was determined in millimeters. Intensity of inflammation and fibrosis was semiquantitatively graded as absent, mild, moderate and severe by 2 independent observers with subsequent analysis by an experienced pathologist who made the final classification. The presence of neoangiogenesis, calcification and adipose metaplasia was defined as absent or present.

Statistical analysis

Categorical variables, expressed as numbers and percentages, were compared using chi-squared testing. Normality of continuous variables was tested using the Shapiro-Wilk test, and data with normal distribution were expressed as mean $\pm$ standard deviation (SD) and differences between inflammation intensity categories, valve area and leaflet thickness were assessed using Student's unpaired t-test. Mean valve area and leaflet thickness were compared in 3 categories of inflammation, using one-way ANOVA test and post hoc analysis with Tuckey's test. Differences that returned P values of <0.05 were considered statistically significant. Statistical analysis was performed using the Statistical Package for Social Sciences for Windows, version 22.0 (SPSS Inc., Chicago, Illinois).

Results

Patient characteristics

The mean age of the patients was 53 ± 13 years and 36 (90%) were females. The characteristics of the study population comparing patients with controls are summarized in Table 1. The majority of the patients were in NYHA functional class III and IV (60%). Figure 1 shows representative pictures of the anatomical characteristics of mitral valves from controls and patients.

Preoperative medications most frequently used were diuretics (60%) and beta-blockers (55%). Patients with atrial fibrillation and/or previous stroke were taking anticoagulants. Thirteen patients (33%) were using penicillin benzathine for secondary prevention of rheumatic fever. The mean age of these patients was 47.9 ± 11.3 . None of the patients

Table 1 – Demographic, clinical and echocardiographic data of the patients who underwent mitral valve replacement due to rheumatic heart disease comparing with controls who underwent heart transplant

Variables*	Rheumatic mitral valves (n=40)	Controls (n=20)	p value
Age (years)	53±13.2	50±11.6	0.334
Female gender	36 (90)	6 (30)	<0.001
Functional class III/IV	24 (60)	16 (80)	0.003
Right-sided heart failure	12 (30)	12 (60)	0.030
Previous mitral valvuloplasty	22 (55)	...	...
Previous history of acute rheumatic fever	27 (68)	...	...
Use of antibiotic prophylaxis	13 (33)	...	...
Atrial fibrillation	24 (60)	5 (25)	0.003
Previous stroke	12 (30)	4 (20)	0.102
Previous hospitalization for heart failure	17 (43)	20 (100)	<0.001
Echocardiographic parameters			
Left ventricular end-diastolic diameter (mm)	51.7±10.9	66.3±7.6	<0.001
Left ventricular end-systolic diameter (mm)	35.8±8.6	57.1±8.2	<0.001
Left ventricular ejection fraction (%)	60.6±10.5	26.5±7.5	<0.001
Mitral valve area (cm ²)	1.18±0.37	...	...
Left atrial diameter (mm)	55.1±10.5	48.9±6.4	0.006
Pulmonary artery systolic pressure (mmHg)	46.5±18.3	39.7±16.8	0.292
Right ventricular dysfunction	16 (40)	9 (45)	0.785

*Data are expressed as mean±SD or number (percentage) of patients.

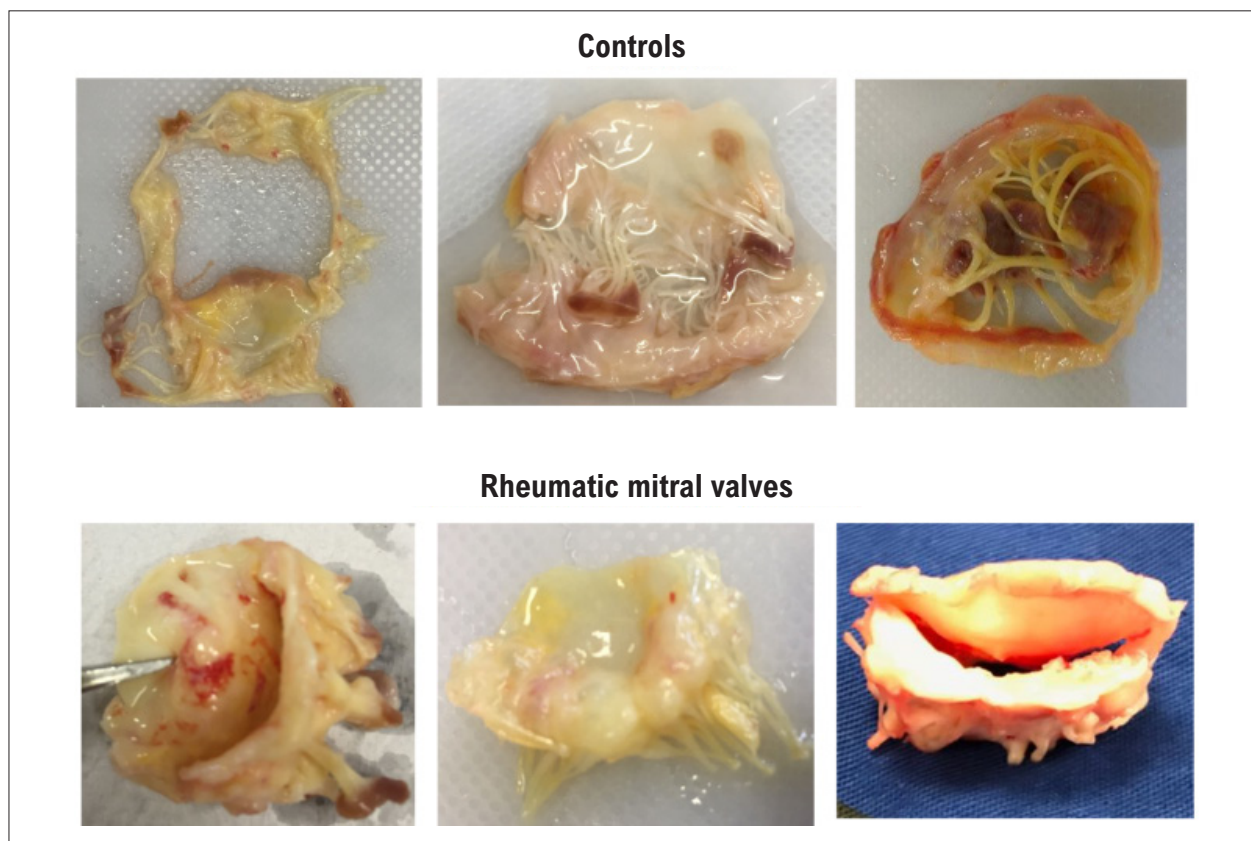


Figure 1 – Gross morphological aspects of the mitral valves from controls and patients with rheumatic heart disease. Note that the in rheumatic valves, and the anterior and posterior mitral leaflets are fused at the commissures. The chordae are shortened and fused.

included in the study had clinical evidence of active acute rheumatic fever.

Regarding the pattern of valve involvement, 18 patients (45%) had pure mitral stenosis, 14 patients (35%) had mixed mitral valve disease, and 8 patients (20%) displayed predominantly mitral regurgitation. Aortic lesion was detected in the echocardiogram of 15 patients (38%). Valvuloplasty had previously been performed in 22 patients (55%), including either percutaneous or surgical intervention. Surgical indication for complications of percutaneous valvuloplasty occurred in 6 patients (15%), 4 of whom due to severe mitral regurgitation related to leaflet or subvalvar apparatus damage. Among those who developed severe mitral regurgitation, 2 patients presented tear of the anterior leaflet and underwent emergency surgery for valve replacement. Two patients had laceration of P3 and A3 scallops in contiguity with posteromedial commissure, and posterior leaflet at central scallop location (P3), respectively, and underwent elective surgery for valve replacement. The other 2 patients presented worsening of mitral regurgitation after the procedure with suboptimal valve opening.

The control group consisted of 20 patients who underwent cardiac transplant, with mean age of 50 ± 12 years, similar to the cases of RHD, with the majority of males (70%). The causes of heart failure were Chagas dilated cardiomyopathy (9 patients), cardiomyopathy after myocarditis (3), ischemic cardiomyopathy (3), idiopathic dilated cardiomyopathy (4) and retransplantation by autoimmune rejection to the graft (1). Secondary moderate to severe mitral regurgitation was found in 7 patients (35%). The other echocardiographic data are shown in Table 1.

Histopathology analysis of rheumatic mitral valves

The endocardium with rheumatic mitral valves was thicker (1.3 ± 0.5 vs. 0.9 ± 0.4 mm) with greater intensity of fibrosis and inflammatory infiltrate compared with controls (Figures 2A and B). The histological findings of rheumatic mitral valves comparing to controls are shown in Table 2. Overall, rheumatic valves presented inflammation of mild intensity, focal distribution and predominance of mononuclear cells, and fibrosis of moderate to severe intensity (Figures 2C and D). Among patients using benzathine penicillin, 9 (69%) had mild inflammation. Neoangiogenesis was more frequent in rheumatic mitral valves than in controls (Figures 2E and F).

None of the valves of the control group presented calcification whereas 35% of rheumatic valves had calcification (Figure 2G). Only a small portion of the valves in both groups had adipose metaplasia (Figure 2H).

According to the type of rheumatic mitral valve lesion, calcification was more frequent in pure mitral stenosis compared with mitral regurgitation or mixed lesions. Histological data according to the predominant mitral valve lesion that required valve replacement are shown in Table 3.

We further stratified the patients into 3 groups according to inflammation intensity in low, moderate and high to correlate with the mitral valve area. We observed that the patients with a higher degree of inflammation and without calcification had a larger mitral valve area (Figures 3 A and B, respectively). There were no differences regarding

leaflet thickness and inflammation intensity (Figure 3C) nor neoangiogenesis and mitral valve area (Figure 3D).

Echocardiographic parameters associated with histological findings

Echocardiographic parameters and histological findings were further compared. We observed an association between left ventricular systolic function, assessed by ejection fraction, and intensity of inflammation. Patients with left ventricular dysfunction, defined by ejection fraction less than 50%, showed a predominance of moderate to marked inflammation compared to patients with preserved ventricular systolic function (50% and 12% respectively, $p=0.023$). While valvular calcification was not associated with left ventricular dysfunction, patients with right ventricular dysfunction had a higher calcification compared with patients with normal right ventricular function (56% and 21% respectively, $p=0.021$), which may be related to the type of lesion associated with calcification.

Discussion

Leaflet tissue inflammation and fibrosis play a central role to induce progressive valve damage in RHD.¹³ The present study evaluated rheumatic mitral valves in the end-stage of RHD when life-threatening valve dysfunction required surgery for valve replacement. The histological findings from rheumatic valves were compared with excised mitral valves from patients who underwent cardiac transplant, without primary valve disease.

Analysis of histological data showed marked fibrosis among all rheumatic valves, showing that continued fibrosis perpetuates throughout RHD progression. The fibrotic state of the mitral valve precedes myocardial dysfunction and manifest heart disease, making it important to develop diagnostic and therapeutic strategies to reduce structural remodeling of heart valves.¹⁹

Notably, even though patients are later in their disease, the valves continue to show active inflammatory processes, predominantly composed of mononuclear cells. The intensity of inflammation was associated with mitral valve area, but not with leaflet thickness. Low inflammatory intensity was found in a smaller valve area, probably due to fibrosis intensity that has an inverse association with the degree of inflammation.

Patients with left ventricular dysfunction presented a higher degree of valve inflammation, which may indicate adjacent myocarditis. However, 4 of the patients with left ventricular dysfunction had mitral insufficiency as the predominant lesion that may be the cause of the left ventricular dysfunction, which is an indication for valve intervention.^{16,17}

Studies indicate that the autoimmune process involved in RHD begins when the reactive antibodies bind to the valvar endothelium, leading to inflammation and cellular infiltration. Once activated, the valvar endothelium increases the expression of adhesion molecules, which facilitates T-cell binding and infiltration.²⁰ After the initial valvar insult, the process triggers a cascade leading to the recognition of additional epitopes, leading to progressive valve damage.²¹ Evidence that continued presentation of autoantigens at the lesion site contributes to an amplification of the immune response is reinforced by

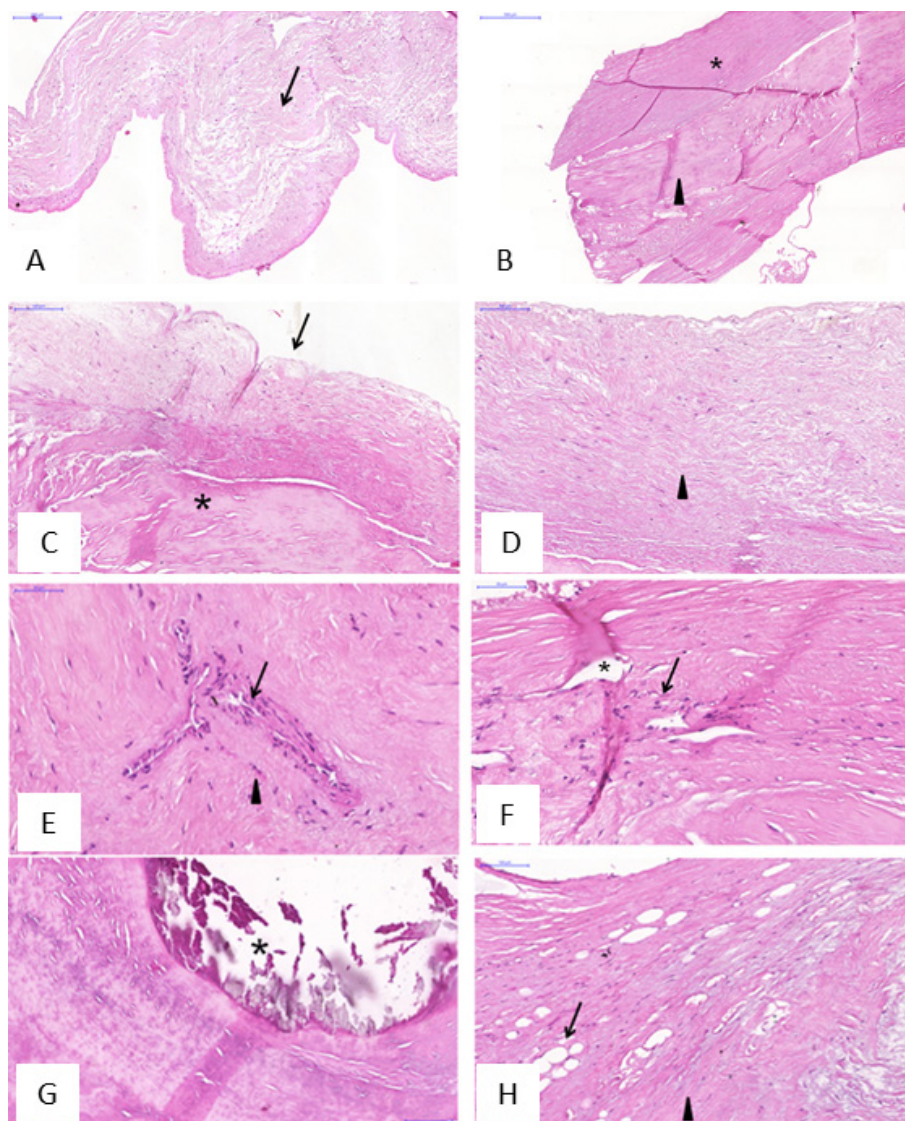


Figure 2 - Representative histological image of mitral valve from controls and rheumatic heart disease patients stained with hematoxylin-eosin. A) Histological view of a control mitral valve, showing mild fibrosis (arrow). B) Rheumatic mitral valve with severe endocardial (asterisk) and interstitial (arrowhead) fibrosis. Panels C-I show specific aspects of mitral valves from rheumatic heart disease patients. C) Presence of endocardium (arrow) and valvar interstitium (asterisk). In the endocardium, there is mild fibrosis. D) Moderate endocardial fibrosis (arrowhead). Staining: hematoxylin-eosin. E) Neovascularization (arrow) with some inflammatory elements (arrowhead). F) Inflammatory foci (arrow) are detectable within neovascularization foci (asterisk). G) Nodular calcification (asterisk). H) Adipose metaplasia (arrow) with areas of fibrosis (arrowhead).

the significant reduction in autoantibody levels after surgical removal of the affected leaflets.²²

After activation of the valvar endothelium with the adhesion of activated T cells, the scarring, neovascularization and lymphocyte infiltration cycle begins.²³ Avascular valvar tissue is normally protected by the endothelium until a triggering factor, which may be antibodies and/or inflammatory cytokines, breaks the endothelial barrier, allowing the cycle of cell infiltration and healing to begin.²⁴ Once initiated, the healing process becomes more intense in the valve interstitium due to

the activation and proliferation of myofibroblasts responsible for valve fibrosis.²⁵ It has already been demonstrated that, in view of some pathological conditions such as RHD, interstitial cells can transform into an activated myofibroblast phenotype, expressing inflammatory proteins and cytokines, capable of rapidly remodeling the extracellular environment.²⁶ The significant decrease in plasma levels of biomarkers of collagen metabolism following mitral valve replacement strongly suggests the contribution of the mitral valve apparatus to the perpetuation of the fibrotic process in RHD.¹⁹

Table 2 – Histological data of rheumatic mitral valves and controls

Variable*		Rheumatic mitral valves (n=40)	Controls (n=20)	p value
Endocardium				
Thickness (mm)		1.3±0.5	0.9±0.4	0.003
Intensity of inflammation	Absent or mild	9 (22)	13 (64)	0.004
	Moderate or severe	31 (78)	7 (36)	
Pattern of inflammation	Focal	31 (78)	7 (36)	0.004
Intensity of fibrosis	Absent or mild	17 (43)	19 (95)	0.001
	Moderate or severe	23 (57)	1 (5)	
Pattern of fibrosis	Even	23 (57)	0	< 0.001
	Uneven	17 (43)	7 (35)	
Neovascularization		11 (28)	0	0.030
Interstitium				
Intensity of inflammation	Absent or mild	33 (82)	14 (72)	0.321
	Moderate or severe	7 (18)	6 (28)	
Pattern of inflammation	Focal	37 (92)	7 (36)	<0.001
Intensity of fibrosis	Absent or mild	0	14 (71)	<0.001
	Moderate or severe	40 (100)	6 (29)	
Pattern of fibrosis	Even	4 (10)	0	0.200
	Uneven	36 (90)	20 (100)	
Neovascularization		24 (60)	7 (35)	0.130
Calcification		14 (35)	0	0.010
Adipose metaplasia		4 (11)	4 (21)	0.320

*Data are expressed as mean±SD or number (percentage) of patients.

Table 3 – Histological findings according to the predominant mitral valve lesion

Variable*		Pure stenosis (n=18)	Regurgitation and combined lesions (n=22)	p value
Inflammation	Absent or mild	15 (83)	18 (82)	0.900
	Moderate or severe	3 (17)	4 (18)	
Neovascularization		11 (61)	13 (59)	0.897
Calcification		10 (56)	4 (18)	0.014
Adipose metaplasia		1 (6)	4 (18)	0.230

*Data are expressed as number (percentage) of patients.

Calcification was detected in 35% of the rheumatic valves, predominantly in pure mitral stenosis, and correlated with valve area. Calcification was also more frequent in patients with right ventricular dysfunction. The identification of calcification reinforces the chronicity of the process, and its occurrence may be related to the mechanisms underlying the end-stage of rheumatic impairment.²⁷ The predominance of calcification observed in rheumatic valves with pure stenosis and in patients with right ventricular involvement confirms that this lesion predominates in the late stages of the disease.³ Rajamannan et al. demonstrated that calcification occurs in areas of neovascularization, stimulated by an active

inflammatory process, formed especially by macrophages and myofibroblasts.²⁸ Banerjee et al. found a greater degree of fibrosis and neovascularization with focal perivascular mild infiltration predominantly of lymphocytes and plasma cells.¹⁹

Study limitations

The small number of patients included in the study is a limitation. However, considering that most rheumatic patients with indication for valve intervention undergo percutaneous valvuloplasty, the number included represents the totality of samples available during the study period.

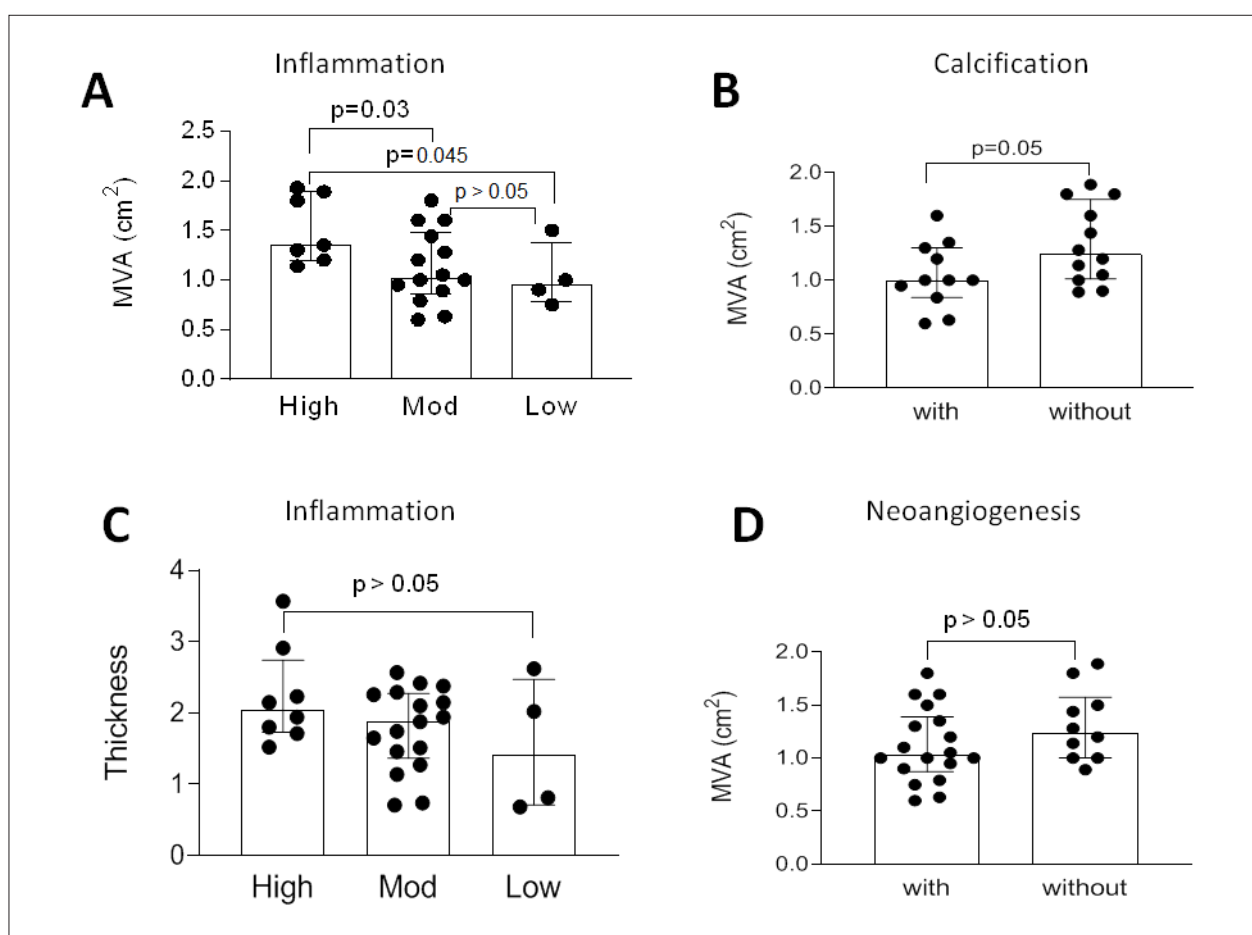


Figure 3 - Associations between histological findings and mitral valve area and leaflet thickness. A) Mitral valve with high and moderate degree of inflammation show higher valve area compared with valves with low degree of inflammation. B) Calcification was associated with mitral valve area, indicating mitral stenosis as a predominant lesion in more calcified valves. C) Association between leaflet thickness and intensity of inflammation. D) Association between neoangiogenesis and mitral valve area.

The high prevalence of atrial fibrillation, previous history of stroke, previous valve intervention, limiting dyspnea (NYHA III and IV) and pulmonary hypertension have been shown to be severe in patients with advanced disease. As we included only patients with indication for valve replacement, our population is, therefore, representative of a spectrum of more severe stages of disease.

Mitral valve replacement is indicated for symptomatic patients with advanced disease and marked valve anatomy deformity, where mitral valve repair is unlikely.²⁹ Therefore, the sample collected for our study represents the advanced rheumatic process, limiting the evaluation of the process in its initial phase.

The valves from the control group are not healthy, normal valves, since they were collected from patients that had undergone heart transplantation due to severe left ventricular dysfunction of different etiologies. Chagas heart disease, the predominant etiology of valves collected from transplanted hearts, is an inflammatory disease, associated with fibrosis. Although Chagas disease primarily affects the ventricular

myocardium, histological valve abnormality may be associated with heart failure.³⁰ In addition, 35% of patients presented moderate to severe secondary mitral valve regurgitation, which may explain abnormal histological findings. The differences in histological analysis could be even greater if compared to healthy tissue valves.

Clinical implications

The pathological process involved in RHD is complex and still not fully understood. The identification of an active chronic inflammatory process, although of mild intensity, probably responsible for the maintenance of immune response and progression of valve lesion, provides subsidy for additional research, aiming to define strategies that can interrupt the progression of valvular damage and its consequences.

Conclusions

Our findings demonstrate that, despite intense degree of fibrosis, the inflammatory process remains active in the rheumatic mitral valves, even at late disease process with valve

dysfunction. This inflammation was associated with mitral valve area and left ventricular function. Valvular calcification was more frequent in mitral stenosis and among patients with right ventricular dysfunction, indicating late and severe rheumatic involvement. It is necessary to better understand what maintains the inflammation and how its persistence may predispose to clinical complications as well as the mechanisms that influence RHD mortality.

Author Contributions

Conception and design of the research: Gomes NFA, Pascoal-Xavier MA, Passos LSA, Passaglia LG, Dutra WO, Nunes MCP; Acquisition of data and Analysis and interpretation of the data: Gomes NFA, Pascoal-Xavier MA, Passos LSA, Paula TMN, Aguiar JMS, Guarçoni FV, Nassif MCL, Gelape CL, Braulio R, Costa PHN, Martins RB, Dutra WO, Nunes MCP; Statistical analysis: Gomes NFA, Passos LSA, Dutra WO, Nunes MCP;

Writing of the manuscript: Gomes NFA, Pascoal-Xavier MA, Passos LSA, Nunes MCP; Critical revision of the manuscript for intellectual content: Gomes NFA, Pascoal-Xavier MA, Passos LSA, Gelape CL, Braulio R, Costa PHN, Passaglia LG, Dutra WO, Nunes MCP.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Study Association

This article is part of the thesis of master submitted by Nayana F. A. Gomes, from Universidade Federal de Minas Gerais.

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Histopathological Characterization of Mitral Valvular Lesions in Patients With Rheumatic Heart Disease: Is Inflammation Also to Blame for Chronic Valvular Heart Disease Progression?

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Short Editorial related to the article: Histopathological Characterization of Mitral Valvular Lesions from Patients with Rheumatic Heart Disease

Rheumatic fever (RF) and rheumatic heart disease (RHD) remain highly prevalent, affecting approximately 40 million people, mostly in low- and middle-income countries, but also in select marginalized populations in higher-income countries.^{1,2} Brazilian data regarding RF prevalence is scarce mainly due to (a) difficulties in acute RF diagnosis, (b) cost of RHD screening and (c) the fact that reported data on surgery or death may represent RF incidence from 2 decades ago. The most feared consequence of RF is valvular heart disease, which leads to a worsening in the quality of life, hospitalizations and need for surgical procedure, primarily in young people.^{3,4} Therefore, there is an urgent need to better understand the factors that influence valvular heart disease (VHD) progression. In this context, Gomes et al.⁵ studied the histopathological changes in mitral valves of patients with RHD undergoing mitral valve replacement.

Inflammation in one of the key components of VHD in patients with RF. In the acute stage of infection, the histopathological findings are the presence of dense valvular inflammatory infiltrates and Aschoff nodules, characterized as collagen fibrinoid degeneration surrounded by lymphocytes, macrophages, giant cells, plasma cells, and palisades of fibroblasts.⁶⁻⁹ Chronic RHD usually presents with cuspid calcification, fibrosis and commissural fusion. However, the role of inflammation in chronic VHD is still under study.

Gomes et al.⁵ examined 60 explanted mitral valves, 40 of rheumatic etiology (53 ± 13 years; 90% females) and 20 from a control group consisting of patients submitted to heart transplant (50 ± 12 years; 70% males). When compared to the control group, rheumatic patients had more fibrosis, neoangiogenesis, calcification and moderate- or severe-intensity inflammation. The presence of an active chronic inflammatory process in the mitral valve requires a better

understanding of rheumatic VHD degeneration progression. Besides, these findings suggest that medical therapeutic options targeting valve inflammation may slow the disease progression in the late stages of VHD. However, two important considerations regarding the study design must be pointed out. First, the study patients and the control group were not matched for several clinical and echocardiographic parameters. Second, it is not possible to rule out that the chronic inflammatory process was a consequence of the hemodynamic stress in the injured valve, and unrelated to the RHD. For this purpose, a control group should consist of patients with non-rheumatic severe valvular heart disease, such as mitral valve prolapse.

In addition, the authors also compared the histopathological findings according to the predominant valve lesion, i.e. stenosis and regurgitation. Mitral stenosis patients had more cuspid calcification, as expected. However, patients with a higher degree of inflammation had a larger mitral valve area. These findings generate 2 hypotheses about the valve injury pattern:

1. Inflammation leads to mitral regurgitation: some patients have more valve inflammation, a larger mitral valve area and thus have a predominance of mitral regurgitation;

2. Inflammation leads to mitral stenosis: as calcification appears, the inflammation is reduced. Hence, patients with less inflammation have smaller valve areas.

Unfortunately, RF is still a marginalized disease with few studies on its pathophysiology. The study carried out by Gomes et al.⁵ provided new important information about inflammation in chronic RHD. However, further research is required to better understand VHD progression, valve injury patterns and, therefore, to establish new treatment options.

Keywords

Mitral Valve Insufficiency/surgery; Rheumatic Heart Disease/diagnosis; Inflammation; Fibrosis; Epidemiology.

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Inhibiting Glucose Metabolism By miR-34a and miR-125b Protects Against Hyperglycemia-Induced Cardiomyocyte Cell Death

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Abstract

Background: It is well-known that insulin resistance and hyperglycemia are important pathological causes for the development of diabetic cardiomyopathy (DCM). However, its precise molecular mechanisms in the pathogenesis of DCM remain unclear.

Objectives: Recent studies reveal that microRNAs (miRNA) play essential roles in the pathogenesis of DCM. This project aimed to determine the roles of miR-34a and miR-125b in hyperglycemia-induced cardiomyocyte cell death.

Methods: Rat primary cardiomyocytes were isolated and exposed to normal and high concentrations of glucose. Cell viability was measured using MTT assay. Expressions of miR-34a and miR-125b were detected by qRT-PCR. Potential targets of miR-34a and miR-125b were predicted from www.Targetscan.org and validated from human heart tissues. A statistical significance of $p < 0.05$ was considered.

Results: The present study shows that miR-34a and miR-125b are downregulated in a human diabetic heart. Moreover, in vitro data from rat primary cardiomyocytes showed that short-term high glucose treatment stimulates miR-34a and miR-125b expressions. Under high glucose, it was found that rat cardiomyocytes displayed increased intracellular glucose metabolism, and glucose uptake and lactate production were significantly increased. It was also found that the key glucose metabolic enzymes, Hexokinase 2 (HK2) and Lactate dehydrogenase-A (LDHA), were direct targets of miR-125b and miR-34a, respectively. Overexpression of miR-125b and miR-34a could prevent hyperglycemia-induced cardiomyocyte cell death. Finally, the restoration of HK2 and LDHA in miR-125b and miR-34a overexpressed cardiomyocytes recovered the cardiomyocytes' sensitivity to hyperglycemia.

Conclusions: Our results proposed a molecular mechanism for the microRNA-mediated diabetic cardiovascular protection and will contribute to developing treatment strategies for diabetes-associated cardiovascular dysfunction. (Arq Bras Cardiol. 2021; 116(3):415-422)

Keywords: Hyperglycemia; Glucose Metabolism Disorders; Cell Death; Diabetic Cardiomyopathies; Myocytes, Cardiac; Rats.

Introduction

Diabetic cardiomyopathy (DCM), which is associated with an increased incidence of heart failure in diabetic patients, is a chronic and irreversible heart complication.^{1,2} It is characterized by complicated pathophysiologic changes in the structure and function of the myocardium, including early diastolic dysfunction, ventricular dilation, and cardiac hypertrophy.^{2,3} DCM is promoted by factors

which are independent from coronary artery disease (CAD), such as insulin resistance in heart tissue, compensatory hyperinsulinemia, and hyperglycemia.⁴ Currently, the precise mechanisms resulting in DCM are still under investigation.

High glucose plays an important role in several diabetic complications including DCM through the induction of inflammatory reactions.⁵ Following uptake by cells, glucose is broken down into pyruvate/lactate, a process called anaerobic glycolysis.⁶ Glycolysis is regulated at several rate-limiting steps, such as glucose uptake, glucose phosphorylation, and conversion of pyruvate into lactate or Acetyl-CoA.⁷ Recent studies reported high glucose inhibition by irisin could influence the development of DCM by regulating the endothelial to mesenchymal transition (EndMT),⁸ suggesting that blocking glycolysis may benefit DCM patients. In addition, another study illustrated metallothionein, an antioxidant, could inhibit the hyperglycemia-induced oxidative stress, resulting in the

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suppression of DCM.⁹ The above reports indicate blocking the hyperglycemia could prevent the DCM. Thus, a better understanding of DCM's pathophysiology will greatly benefit early diagnosis and the treatment for diabetes-associated cardiovascular dysfunction.

MicroRNA, a small (~20-25 nt) and highly conserved non-coding RNA, has proved to play critical roles in cardiac remodeling and the development of heart failure,^{10,11} suggesting a potentially therapeutic target for the diagnosis and treatment of DCM. Among microRNAs, which have been reported to be significantly altered during DCM, miR-34a tends to be upregulated during DCM,¹¹ while miR-125b is known to be associated with hypertrophic growth,¹² indicating that miR-34a and miR-125b are involved in the development of DCM. However, whether miR-125b and miR-34a could regulate the hyperglycemia-induced cardiomyopathy remains unclear. Therefore, the present study seeks to investigate the potential role and mechanism of miR-34a and miR-125b in hyperglycemia-induced cardiomyocyte dysfunction, suggesting a new therapeutic strategy in the management of DCM.

Methods

Rat cardiomyocyte culture

The isolation of rat cardiomyocytes was performed following prior study.¹³ Briefly, rat cardiomyocytes were collected from day two postnatal rat hearts. In total, eight rats were dissected, and the isolated/cultured cardiomyocytes from all rat hearts were pooled. All experiments were performed using the same cells from the pool. The cardiomyocytes were further identified by staining the smooth muscle actin, sarcomeric alpha-actinin, and tropomyosin. The cardiomyocytes were cultured with specific cardiomyocyte medium (Catalog No. 6201; ScienCell), according to manufacturer's instructions. The culture medium was refreshed every 24 hours. Seventy-two hours later, cell culture medium was changed to serum-free Dulbecco's modified Eagle's medium (DMEM, Catalog No. 31600-034; Invitrogen Corporation, Grand Island, NY, USA), together with 10% Fetal Bovine Serum (FBS) and 1% penicillin/streptomycin in a humidified atmosphere of 5% CO₂ at 37°C. Rat cell experiments were performed in triplicate and repeated three times. The animal experiments were performed after having received approval from the Animal Ethical Review Board of Heilongjiang Province Hospital (No. AHPH-201711-06).

Human heart tissue samples

Human heart tissue samples were obtained from failing human hearts with DCM (20 cases) at the time of transplant at the Heilongjiang Province Hospital. Tissues were frozen immediately in liquid nitrogen and were then stored at -80°C until use. Normal hearts (20 cases) were obtained from healthy donors without transplants and stored by the same procedures. Human tissue collection was performed after having received approval from the Ethical Review Board of Heilongjiang Province Hospital (No. PH-201706-2H). Informed consent was obtained from all patients.

Plasmid DNA and microRNA precursor transfection

MiR-34a precursor, miR-125b precursor, and negative control were purchased from Genepharma (Shanghai, China). MicroRNA precursors and negative control microRNA were transfected at 50 nM. Cells were seeded in 6-well plates at 10⁵ densities 24 h prior to transfection. Transfection was performed using the Lipofectamine RNAiMax Transfection Reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's instructions. After 72 h, the cells were collected for downstream analysis. Overexpression vectors containing human ORF LDHA, or HK2, were purchased from Origene Technologies Inc. (Rockville, MD) and 4 µg of plasmid was transfected using the Lipofectamine 2000 transfection reagent (Invitrogen, Carlsbad, CA, USA) according to the manufacturer's protocol. Cells were collected after 48 hours for downstream analysis.

Glucose uptake and lactate production

The glucose uptake assay was performed using the Glucose Uptake Colorimetric Assay Kit (#MAK083) from Sigma (Shanghai, China), according to manufacturer's instructions. The lactate production was detected using the Lactate Assay Kit (#MAK064) from Sigma (Shanghai, China), according to manufacturer's instructions. Data were normalized by the cell numbers of each experimental group. Assays were performed in triplicate and repeated three times.

Detection of cardiomyocyte cell death

The cardiomyocyte cell death was investigated by the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay and verified by direct Trypan blue staining. Briefly, 24 hours after treatments with high glucose, the cell culture medium was replaced with 200 µL fresh medium and 20 µL of 5 mg/mL MTT (Sigma, #M5655) was put into the rat cardiomyocytes for 2 hours at 37°C. The culture medium was completely removed, and 100 µL of DMSO was added. Plates were put on an orbital shaker for 5 minutes at room temperature. The absorbance, at optical density (OD) of 590 nm, was measured. This absorbance was normalized by cell numbers of each well. Each experiment was performed in triplicate and repeated three times.

Quantitative RT-PCR

Total RNA was isolated from tissue and cardiomyocyte cells, using the TRIzol Reagent (Invitrogen, Carlsbad, CA) according to manufacturer's instructions. After DNase treatment, the quality of the RNA was measured by NanoDrop. To detect the miRNAs, a polyA tail was conjugated to the RNase-free DNase digested RNA, and qRT-PCR was performed using the qRT-PCR miRNA Detection Kit (Applied Biosystems), following manufacturer's instructions. Human U6 served as an internal control. Quantitative polymerase chain reaction (qPCR) was performed using SYBR Green Taq ReadyMix (Sigma) on an Applied Biosystems 7500 PCR system. Results

were analyzed using the $2^{-\Delta\Delta Ct}$ method and normalized to U6 expression. All qRT-PCR assays were performed with the Bio-Rad IQTM5 Multicolour Real-Time PCR Detection System. Experiments were performed in triplicate and repeated three times.

Target prediction

The potential targets of miR-125b and miR-34a were computationally predicted by the TargetScan program (<http://www.targetscan.org/>).

Western blot analysis

Western blot analysis was performed to assess the expressions of HK2 and LDHA proteins. Cell lysates from rat cardiomyocytes were extracted using RIPA Lysis and Extraction Buffer (#89900, Thermo Scientific, Shanghai, China). Protein concentration was determined by applying the Bradford method, as previously described.¹⁴ An equal amount of protein sample was loaded on a 10% SDS-PAGE gel, followed by electrophoresis, and transferred onto a nitrocellulose membrane. Membranes were blocked by 5% BSA for one hour at room temperature. After complete washing by TBST, the blots were incubated with primary antibodies, all from Cellsignaling Technology (Danvers, MA, USA) (HK2, #2867; LDHA, #3582 and α -tubulin, #2125) at 1:1000 for overnight at 4°C. Membranes were washed and incubated with respective secondary antibodies at 1:3000 for 1 hour at room temperature. Bands were detected by chemiluminescence developing agents (SuperSignal, Thermo Scientific). Results were repeated three times, and representative figures were shown.

Statistical analysis

Statistical analysis was performed using the GraphPad Prism 5 software (GraphPad Software, Inc., La Jolla, CA, USA). The unpaired Student's t-test was used for data analysis between two groups. The significance among three or more groups was analyzed by ANOVA. Data was presented as mean and standard deviation. The error bars in graphs represented standard deviation. Correlations between variables were determined by Pearson's correlation coefficient. Experiments were performed in triplicate and repeated three times. Data from rat cardiomyocyte experiments were normalized by the cell number of each experimental group. α -tubulin was an internal control for Western blot. U6 was an internal control for qRT-PCR. $p < 0.05$ was considered statistically significant.

Results

Down-regulation of miR-34a and miR-125b in a human diabetic heart

To evaluate the roles of miRNAs in a human diabetic heart, miR-34a and miR-125b expression levels were examined in human heart tissues obtained from 20 patients with diabetic heart failure and 20 healthy donors. The expressions of miR-34a and miR-125b were significantly downregulated in heart tissues with diabetic heart failure, when compared with those

from healthy donors (Figure 1A and 1B). These results suggest a protective role of miR-34a and miR-125b during high glucose-mediated heart failure.

Short-term high glucose stimulates miR-34a and miR-125b expressions in neonatal rat cardiomyocytes

To evaluate the effect of miR-34a and miR-125b in high glucose-induced cardiomyocyte dysfunction, this study established an *in vitro* model using the isolated rat cardiomyocytes cultured under normal and high glucose conditions. Interestingly enough, within a short period of time (1 hour), miR-34a and miR-125b were found to be significantly induced by 25 or 50 mM high glucose concentration (Figure 1C and 1D). However, under long time hyperglycemia (48 hours, 50 mM), cardiomyocytes underwent cell death (data not shown). Taken together, the above results revealed an adaptive upregulation of miR-34a and miR-125b by hyperglycemia in cardiomyocytes.

Overexpression of miR-34a and miR-125b protects against hyperglycemia-induced cardiomyocyte death

It is well-known that hyperglycemia can trigger inflammatory responses and induce cardiomyocyte cell death (4). It was therefore asked whether exogenous overexpressing miR-34a and miR-125b could protect against hyperglycemia-induced cardiomyocyte death. Rat cardiomyocytes were co-transfected with pre-miR-34a and pre-miR-125b for 48 hours. qRT-PCR results showed miR-34a and miR-125b expressions were increased by 5-10 folds (Figure 2A). Cells were then exposed to 25 or 50 mM glucose to mimic hyperglycemia for 48 hours. Expectedly, control miRNA transfected cardiomyocytes presented a clear cell death under HG treatment (Figure 2B). However, cardiomyocytes with miR-34a and miR-125b overexpression proved to be significantly resistant to HG when analyzed by both MTT assay and Caspase-3 activity assay (Figure 2B and 2C). These results demonstrated a protective role of miR-34a and miR-125b in HG-induced cardiomyocyte cell death.

Inhibition of glycolysis by miR-34a and miR-125b under hyperglycemia by targeting LDHA and HK2

Under high glucose, cells exhibited an increased cellular glucose metabolism.^{6,7} To investigate the mechanisms underlining the roles of miR-34a and miR-125b during HG treatments, a literature review was performed and recent studies were found that showed both miR-34a and miR-125b could inhibit intracellular glucose metabolism.^{15,16} Thus, it was hypothesized that the inhibition of the HG-activated intracellular glycolysis by miR-34a and miR-125b contributes to protecting cardiomyocytes against cell death. To assess the inhibitory effects of miR-34a and miR-125b on glycolysis under hyperglycemia, the glucose uptake and lactate production of cardiomyocytes with or without miRNAs overexpression were measured in normal or high glucose treatments. Overexpression of miR-34a and miR-125b inhibited glucose uptake and lactate production under normal glucose (Figure 3A and 3B). In addition, cardiomyocytes with high miR-34a and miR-125b also displayed significantly decreased glycolysis,

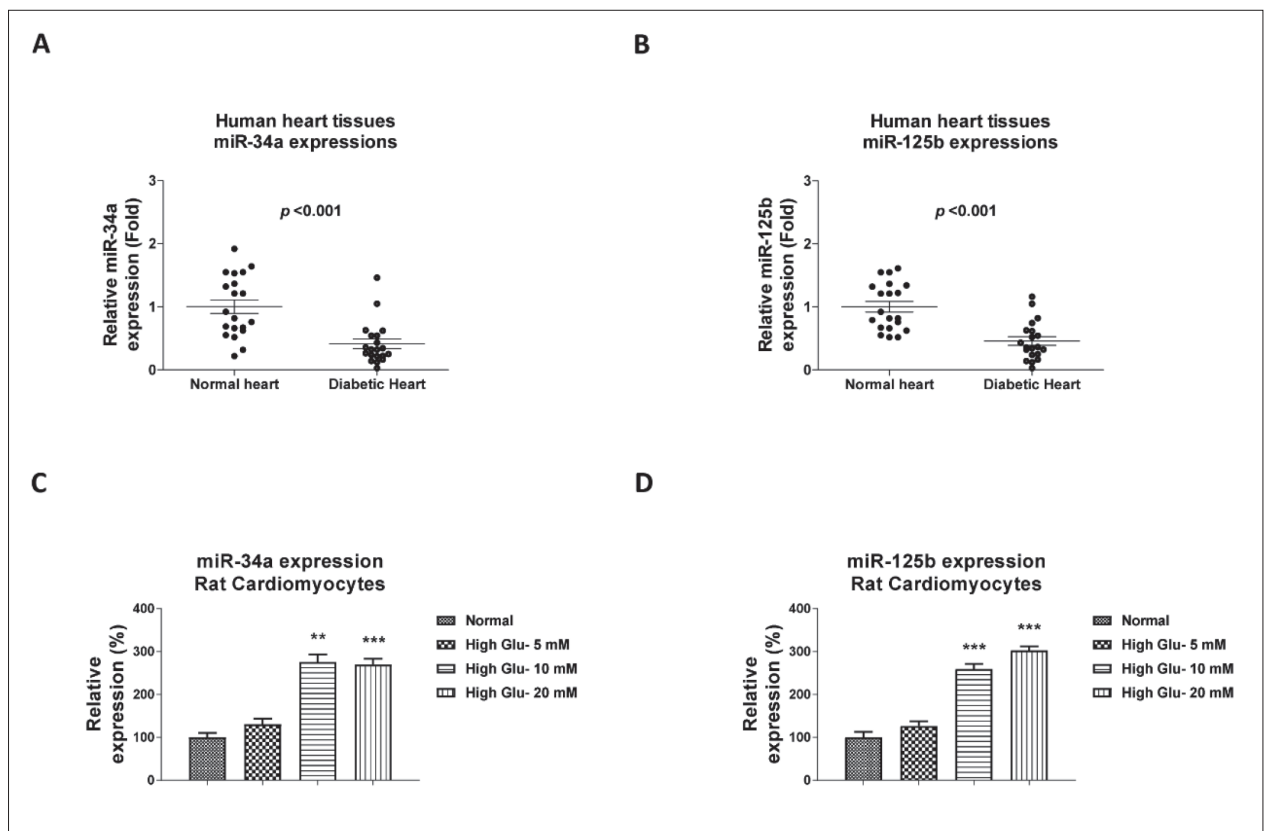


Figure 1 – Down-regulation of miR-34a and miR-125b in a human diabetic heart, induced by hyperglycemia. (A) Expressions of miR-34a and (B) miR-125b in a normal human heart and diabetic heart tissues. (C) Rat cardiomyocytes were treated with control or high glucose at 5, 10, or 20 mM. The relative expressions of miR-34a and (D) miR-125b were assessed by real-time PCR and normalized to U6 snRNA levels. Columns, mean of three independent experiments; the error bars in graphs represented SD. $**$, $p < 0.01$; $***$, $p < 0.001$.

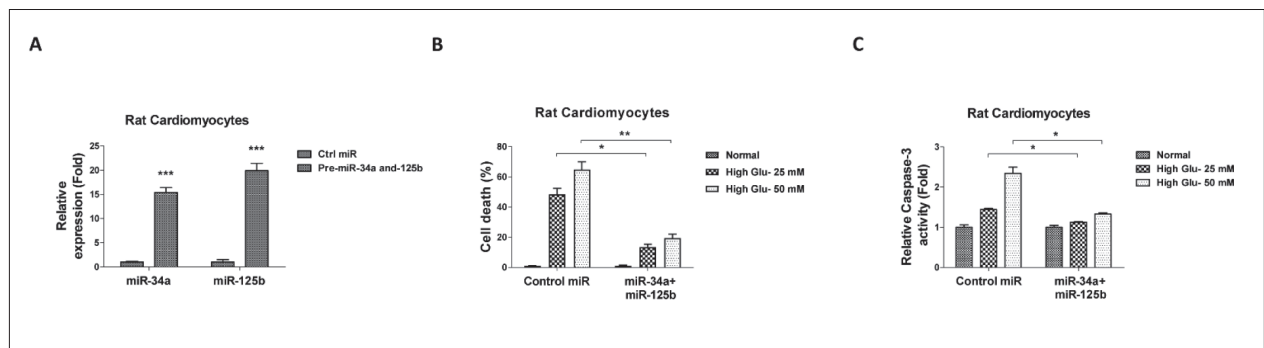


Figure 2 – Overexpression of miR-34a and miR-125b protects against hyperglycemia-induced cardiomyocytes death. (A) Rat primary cardiomyocytes were transfected with control microRNA, or pre-miR-34a plus miR-125b for 72 hours. The expressions of miR-34a and miR-125b were measured by qRT-PCR. (B) Rat primary cardiomyocytes were transfected with control microRNA, or pre-miR-34a plus miR-125b for 72 hours; cells were exposed under normal or high glucose (25 mM or 50 mM) for 48 hours. The cell apoptosis rate was measured by MTT assay and (C) Caspase-3 activity. Columns, mean of three independent experiments; the error bars in graphs represented SD. $*$, $p < 0.05$; $**$, $p < 0.01$; $***$, $p < 0.001$.

close to the normal levels (Figure 3A and 3B), suggesting that an overexpression of miR-34a and miR-125b under hyperglycemia contributes to the maintenance of intracellular glucose homeostasis. To verify the direct targets of miR-34a and miR-125b in cardiomyocytes, we detected the protein expressions of LDHA, which is a predicted target of miR-34a

and HK2, the 3'UTR of which could be directly targeted by miR-125b (Figure 4A). Western blot results consistently showed the protein levels of HK2 and LDHA were suppressed by an overexpression of miR-34a and miR-125b under both normal and HG conditions (Figure 4B). The targets of miR-34a and miR-125b were further verified in human heart tissues.

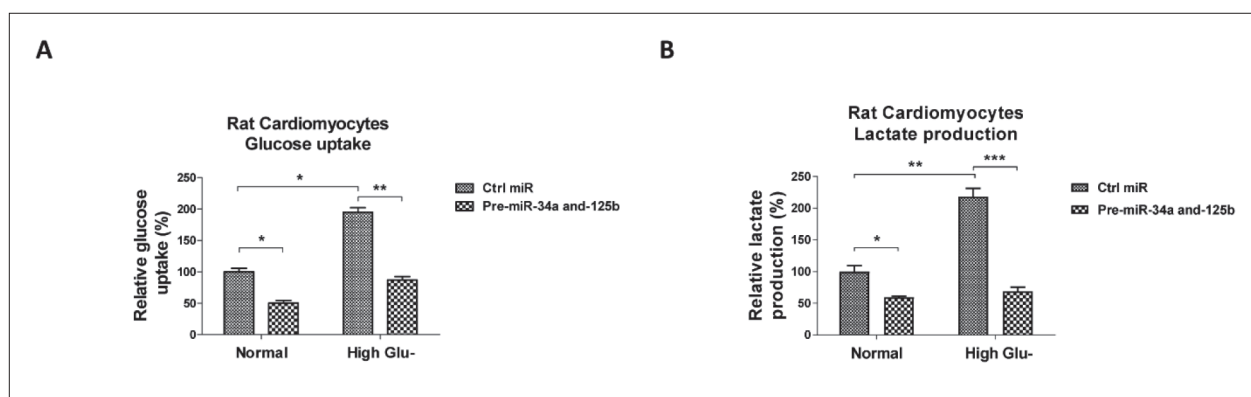


Figure 3 – Overexpression of miR-34a and miR-125b impairs hyperglycemia-induced glucose metabolism. (A) Rat primary cardiomyocytes were transfected with control microRNA, or pre-miR-34a plus miR-125b for 72 hours; cells were exposed under normal or high glucose (25 mM) for 48 hours. Glucose uptake and (B) lactate production were measured. Columns, mean of three independent experiments; the error bars in graphs represented SD. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

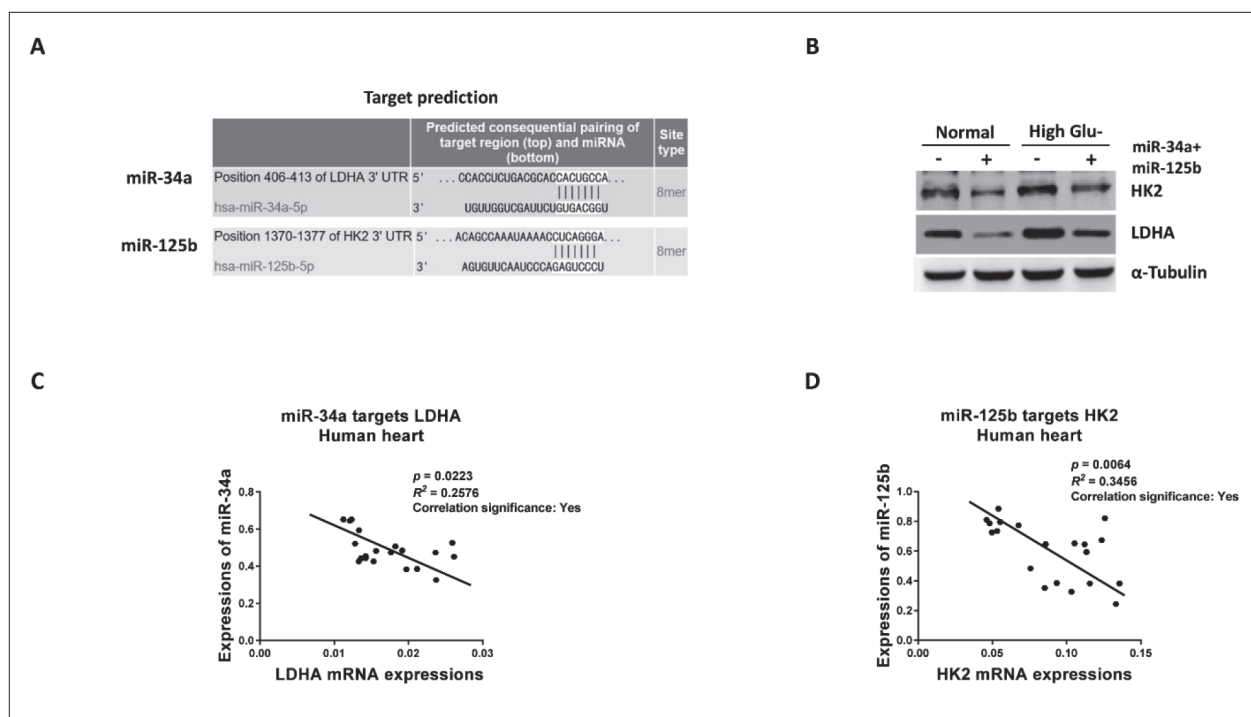


Figure 4 – miR-34a and miR-125b target glycolysis enzymes in cardiomyocytes and heart tissues. (A) illustration of LDHA 3'UTR and HK2 3'UTR, as well as the seed sequence of miR-34a and miR-125b, showing the computationally predicted target region on the 3'UTR of LDHA and HK2 mRNAs. (B) Rat cardiomyocytes were transfected with 25 nM miR-34a plus miR-125b precursors for 72 h. Overexpression of miR-34a plus miR-125b downregulated LDHA and HK2 protein expressions under normal and high glucose conditions. α -Tubulin was a loading control. (C) Negative correlation between miR-34a and LDHA mRNA expressions in normal human heart tissues. (D) Negative correlation between miR-125b and HK2 mRNA expressions in normal human heart tissues.

In a consistent manner, in miR-34a and miR-125b, whose expression is relatively high in normal heart tissues, the mRNA levels of HK2 and LDHA were apparently low (Figure 4C). The same negative correlation between miR-34a and LDHA, miR-125b, and HK2 was observed in diabetic heart tissues (Figure 4D). In general, our data support that the miR-34a and miR-125b inhibit intracellular glycolysis by targeting glycolysis

speed limited enzymes, contributing to the maintenance of glucose homeostasis under hyperglycemia.

Restoration of LDHA and HK2 sensitizes cardiomyocyte to high glucose

Finally, to test whether the protection of cardiomyocytes under HG was directly caused by glycolysis inhibition by miR-

34a and miR-125b, rescue experiments were performed by co-transfection of LDHA and HK2 overexpression plasmids into miR-34a and miR-125b overexpressing cardiomyocytes. Western blot results (Figure 5A) showed that the co-transfection of plasmids successfully rescued the LDHA and HK2 expressions in miR-34a and miR-125b overexpressing cardiomyocytes. Furthermore, the glucose uptake (Figure 5B) and lactate production (Figure 5C) were also recovered to normal levels by restoration of LDHA and HK2. The above transfected cells were exposed to 50 mM glucose to mimic hyperglycemia for 48 hours. Cells were collected and subjected to cell death assay. As expected, cardiomyocytes with LDHA and HK2 rescue showed significantly increased cell death under hyperglycemia, as compared to that of miR-34a and miR-125b overexpressing cardiomyocytes (Figure 5D). These rescue experiments supported the miR-34a and miR-125b-mediated intracellular glucose homeostasis in hyperglycemia directly protected by cardiomyocytes.

Discussion

DCM is one of the major health threats in patients with diabetes.^{1,2} It is associated with complex pathophysiologic events, including chronic inflammation and cardiac cell death, eventually resulting in heart failure. The early cardiac response to diabetes was apoptotic cardiomyocyte death.³ The present study reported on a microRNA-mediated cardiomyocyte protection mechanism under hyperglycemia. Rat cardiomyocytes were treated with high glucose, identifying a significant increased glycolysis, a process regulated by the adaptively upregulated miR-34a and miR-125b, indicating that the targeting of hyperglycemia-induced glucose metabolism by miR-34a and miR-125b might contribute to the development of a therapeutic method to protect against cardiac cell death.

Glucose and acute insulin resistance have been found in acute cardiac conditions.⁴ Furthermore, high intracellular glucose metabolism has been recognized as a potential prognostic marker in acute coronary syndromes.¹⁷ The

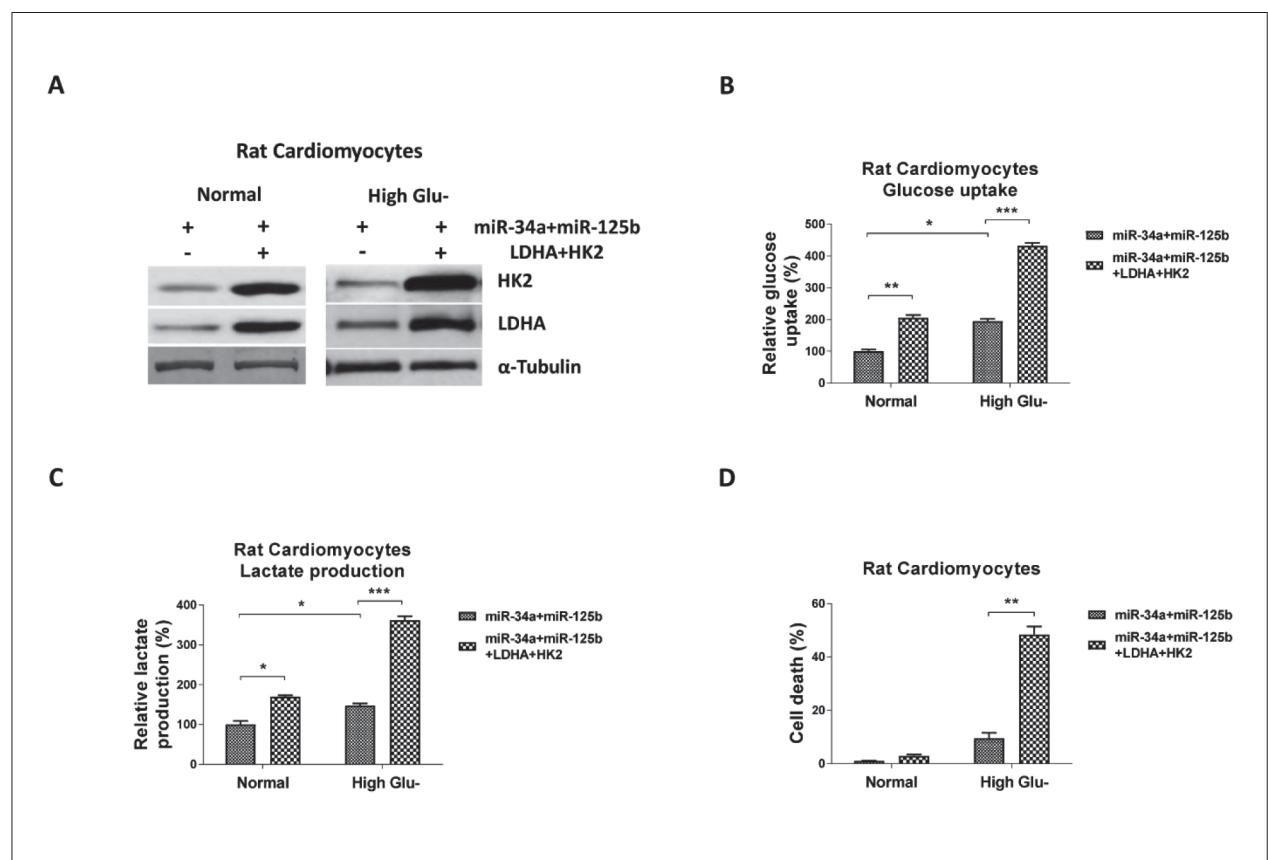


Figure 5 – Restoration of glycolysis in miR-34a and miR-125b overexpressed rat cardiomyocyte promotes cell death under hyperglycemia. (A) Rat cardiomyocytes were transfected with miR-34a plus miR-125b mixture alone or co-transfected with miR-34a plus miR-125b and LDHA plus HK2 overexpression plasmids for 72 hours. Cells were then treated with or without high glucose (25 mM) for 48 hours and subjected to Western blot analysis. α -Tubulin was a loading control. (B) Rat cardiomyocytes were transfected with miR-34a plus miR-125b mixture alone or co-transfected with miR-34a plus miR-125b and LDHA plus HK2 overexpression plasmids for 72 hours. Cells were then treated with or without high glucose (25 mM) for 48 hours. Glucose uptake and (C) lactate production were measured. (D) Rat cardiomyocytes were transfected with miR-34a plus miR-125b mixture alone or co-transfected with miR-34a plus miR-125b and LDHA plus HK2 overexpression plasmids for 72 hours. Cells were then treated with or without high glucose (50 mM) for 48 hours. Cell death was assessed by MTT assay. Columns, mean of three independent experiments; the error bars in graphs represented SD. *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.

association between hyperglycemia and DCM has been extensively studied.¹⁸ Abnormal insulin metabolic signaling, hyperglycemia, mitochondrial dysfunction, and oxidative stress are the most recognized pathophysiological mechanisms involved in the development of DCM.¹⁸ Currently, the underlying molecular mechanisms resulting in DCM are poorly understood. Recent studies have shown that microRNAs play essential roles in the etiology of diabetes and its complications.¹¹ Moreover, miR-125b and miR-34a have proven to be associated with the oxidative stress of cardiac tissues, leading to prevent against cardiomyocytes cell death.¹¹ In cancers, miR-34a and miR-125b have been reported to downregulate and inhibit glucose metabolism,^{15,19} suggesting that miR-34a and miR-125b could regulate the dysfunctional cells under hyperglycemic conditions. Our results demonstrated that miR-34a and miR-125b were significantly downregulated in human diabetic heart tissues, when compared with a normal heart. It was also found that miR-34a and miR-125b were adaptively stimulated under high glucose conditions in rat cardiomyocytes, suggesting that miR-34a and miR-125b might suppress the hyperglycemia-induced intracellular glucose metabolism. It is well-known that miR-34a could target 3'UTR of LDHA mRNA²⁰ and that HK2 is a direct target of miR-125b in cancer cells.¹⁹ This study has some limitations in confirming the effects of the miRNAs on the DCM protection from *in vivo* data. Our data, however, has, for the first time, revealed that miR-34a and HK2 could suppress glucose uptake and lactate production in cardiomyocytes. Overexpression of miR-34a and miR-125b contributed to the maintenance of intracellular glucose metabolism under hyperglycemic conditions (Figure 3).

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Conclusion

In summary, the present study demonstrated that miR-34a and miR-125b were significantly correlated with human DCM. Using an *in vitro* rat cardiomyocytes model, hyperglycemia adaptively stimulated miR-34a and miR-125b expressions. The overexpression of miR-34a and miR-125b suppressed high glucose-induced intracellular glucose metabolism by targeting LDHA and HK2, resulting in the prevention of the hyperglycemia-induced cardiomyocyte cell death. Taken together, this study serves to reveal the potential roles of miR-34a and miR-125b in the pathogenesis of hyperglycemia-induced cardiomyopathy. Our future work will focus on an *in vivo* rat diabetic model to investigate the molecular mechanisms of miR-34a and miR-125b in DCM.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Statistical analysis: Chao-rui X; Writing of the manuscript: Chao-rui X.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

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Study Association

This study is not associated with any thesis or dissertation work.

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Cardiovascular Risk Estimates in Ten Years in the Brazilian Population, a Population-Based Study

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Abstract

Background: Cardiovascular diseases are the leading cause of morbidity and mortality, resulting in high health costs and significant economic losses. The Framingham score has been widely used to stratify the cardiovascular risk of the individuals, identifying those at higher risk for the implementation of prevention measures directed to this group.

Objective: To estimate cardiovascular risk at 10 years in the adult Brazilian population.

Methods: Cross-sectional study using laboratory data from a subsample of the National Health Survey. To calculate cardiovascular risk, the Framingham score stratified by sex was used.

Results: Most women (58.4%) had low cardiovascular risk, 32.9% had medium risk and 8.7% had high risk. Among men, 36.5% had low cardiovascular risk, 41.9% had medium risk and 21.6% had high risk. The risk increased with age and was high in the low-educated population. The proportion of the components of the Framingham model, by risk and sex, shows that, among women at high risk, the indicators that mostly contributed to cardiovascular risk were: systolic blood pressure, total cholesterol, HDL, diabetes and tobacco. Among men, systolic blood pressure, total cholesterol, HDL, tobacco and diabetes.

Conclusion: The study estimates, for the first time in Brazil, the risk of developing cardiovascular disease in ten years. The risk score is useful to support the prevention practices of these diseases, considering the clinical and epidemiological context. (Arq Bras Cardiol. 2021; 116(3):423-431)

Keywords: Cardiovascular Diseases; Risk Factors; Cholesterol; Atherosclerosis; Diabetes Mellitus, Hypertension; Epidemiology.

Introduction

Cardiovascular diseases (CVD) were responsible for approximately 17.9 million deaths in 2016, nearly 31% of the total deaths worldwide, constituting the most frequent cause of morbidity and mortality rates.¹⁻³ Also in Brazil, in 2016, CVDs presented the highest mortality rates and disability-adjusted life years (DALYs), in both sexes.^{4,5} CVDs also stand out due to their high hospitalization and treatment costs in the Brazilian public health system (SUS, in Portuguese), in addition to the indirect costs caused by the reduction in productivity, medical leave from work, and the negative effects upon the quality of life of the affected individuals and their family members.⁶

The Framingham Heart Study (a cohort study), which began in 1948, was the first to identify the association between the

main risk factors (RF) (hypertension, high cholesterol levels and smoking) and coronary disease.⁷ In the sequence of these findings, guidelines and protocols arose, which focused on a single RF, such as hypertension,⁸ or cholesterol,⁹ for the prevention of CVD. In 1993, studies from New Zealand were the first to use multiple risk factors in determining cardiovascular risk.¹⁰ Conducted by the Framingham team, the studies proposed a systematization by sex and age range, which predicted the risk of coronary disease development in the coming decade, considering the scores calculated using systolic blood pressure, total cholesterol, HDL cholesterol, diabetes, and smoking.^{10,11}

The proposal of Framingham algorithms to predict CVD was incorporated into the Third Report of the Panel of Specialists in the detection, evaluation and treatment of high cholesterol (Adult Treatment Panel III), in 2001.¹² What followed was the validation of these algorithms in black and white individuals in the United States,^{13,14} in various populations of Europe, the Mediterranean region, Asia, and throughout the world, with good outcomes.¹⁵⁻¹⁹

Other adaptations followed, most notably for the Overall Cardiovascular Risk, in 2008, proposed by the Framingham group,²⁰ seeking to estimate the risk of cardiovascular events over a 10-year period, such as coronary artery disease

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(CAD), stroke, occlusive peripheral arterial disease (OPAD) or heart failure, over a 10-year period.²⁰ This score has been frequently used worldwide and has also been used in Brazil, following Brazilian guidelines, to understand and estimate the absolute CV risk over a 10-year period.²¹ These scores allow for preventive actions, especially since they guide the population-based strategy to search for and identify high risk, seeking opportunities for their prevention.²²

In an attempt to understand the health profile of the Brazilian population, the Ministry of Health and the Brazilian Institute of Geography and Statistics (IBGE) conducted the National Health Survey (NHS), a broad household survey that gathered information on a national scale about the population. This questionnaire included information about CVD risk factors. In 2014 and 2015, laboratory exams were collected to make advancements in cardiovascular risk (CVR) assessments representative of the Brazilian population, considering that previous estimations have been based on specific population studies, such as hospital studies²³ or cohort studies among employees from Brazilian universities.²⁴

Therefore, the present study sought to estimate CVR over a 10-year period in the Brazilian adult population, according to NHS laboratory data.

Methods

This is a cross-sectional study conducted by means of secondary data from the NHS, a Brazilian household survey, as part of the Integrated System of Household Surveys (ISHS), from IBGE.^{25,26} The laboratory component was collected in 2014 and 2015, and the NHS sampling and the laboratory subsample methodologies can be found in previous studies.^{25,27,28} The laboratory subsample included 8,952 people and, taking into account the correction for possible biases in the statistical analyses, post-stratification weights were used, according to sex, age, level of education, and region.^{28,29} The weighting procedure used variables from both the samples and the reference population, obtained from external sources, according to data from the 2010 IBGE Census, to adjust the distribution of the collected sample in the household survey to that found for the complete groups of the Brazilian population. The choice of variables used in the construction of weights took into consideration the characteristics of the excluded population to minimize the representation bias. In this sense, using the post-stratification weights, the laboratory sample becomes representative of the Brazilian adult population.^{28,29}

The blood collected in the laboratory was centrifuged, and the serum and plasma samples were stored in a refrigerator at 4 °C and analyzed by automated and regularly calibrated equipment. Among the collected exams, glycated hemoglobin (HbA1c) was collected in a tube with ethylenediaminetetraacetic acid (EDTA) and dosed by High Pressure Liquid Chromatography (HPLC). This study used the cutoff point established by the World Health Organization (WHO), while the American Diabetes Association recommended HbA1c $\geq 6.5\%$ for the diagnosis of diabetes mellitus (DM).²⁹ Total cholesterol (TC) and high-density lipoprotein (HDL) were collected in a gel tube and the values for the Brazilian population were calculated.³⁰

Blood pressure was measured after explanation of the procedure to the patient, who was supposed to rest for at least five minutes in a calm environment; not have a full stomach; not have practiced physical exercise for 60 to 90 minutes prior; not have ingested alcoholic beverages, coffee or food; not have smoked for 30 minutes prior; maintaining legs crossed, feet on the ground, back resting on a chair, relaxing and not speaking during the measurement.³¹ In total, three measurements were taken, with intervals of two minutes between each, using a calibrated mercury column sphygmomanometer. At the end, the three measurements were recorded as the definitive value for data analysis.

Smoking was evaluated through the following questions: "Are you or have you ever been a smoker, that is, have you smoked at least 100 cigarettes throughout your life?" and "How many cigarettes do you currently smoke per day?"

The scoring to estimate the overall CVR followed that proposed by Framingham²⁰ and considered sex, age, TC and HDL cholesterol, treated and untreated blood pressure, smoking (yes or no), diabetes (yes or no). Separate calculations were performed for men and women. The specific risks were calculated by age and considered the frequency rates (FR) described below.²⁰ Individuals younger than 30 and older than 74 excluded from the analysis, maintaining the same age groups of the cohort used in the risk estimation.²⁰ Likewise, individuals who declared that they had been diagnosed by a doctor with heart disease or stroke (also known as a cerebrovascular accident – CVA) were excluded from this analysis.

The scores considered that proposed by D'Agostino et al.,²⁰ detailed in another publication,²⁰ and which was adopted in Brazil, in 2013, by the Brazilian Society of Cardiology, entitled the Global Risk Score (GRS).²¹ Age was self-reported by the participants and considered the following age ranges: 30–34, 35–39, 40–44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, 75 and over. The male scores ranged from 0 to 15 points and the female scores ranged from 0 to 12 points.

Male smokers presented scores of 4 points, while female smokers presented scores of 3 points. Blood pressure (BP) attributed a differential score between those that were and those that were not undergoing drug treatment, considering the question: "Have you used any high blood pressure drugs in the last 15 days?". The male score ranged from -2 to 3 (under treatment) and 0 to 4 (without treatment), and the female score ranged from -1 to 7 (under treatment) and -3 to 5 (without treatment).²⁰

Regarding laboratory exams, the cutoff points and estimation scores were:

a) Diabetes: hemoglobin was used (HbA1c $< 6.5\%$ = 0 for both sexes; HbA1c $\geq 6.5\%$ men = 3 points, women = 4 points), or disease diagnosis by a doctor.

b) CT: For women: CT < 160 mg/dl = 0 points, CT 160–199 mg/dl = 1 point, CT ≥ 200 –239 mg/dl = 3 points, CT ≥ 240 –279 mg/dl = 4 points, CT ≥ 280 = 5 points). For men: CT < 160 mg/dl = 0 points, CT 160–199 mg/dl = 1 point, CT ≥ 200 –239 mg/dl = 2 points, CT ≥ 240 –279 mg/dl = 3 points, CT ≥ 280 = 4 points).

c) HDL cholesterol for men (≥ 60 mg/dL = -2 points, HDL 50–59 = -1 point, HDL 45–49 = 0 points, 35–44 = 1, < 35 mg/dL = 2 points). For women: ≥ 60 mg/dL = -2 points, HDL

Original Article

50–59 mg/dL = -1 point, HDL 45–49 = 0 point, 35–44 = 1, <35 mg/dL = 2 points).

The study estimated the overall GRS for men and women and the respective confidence intervals (95% CI). The analyses were carried out using Stata, version 13. According to the guidelines set forth by the Brazilian Society of Cardiology, the following cutoff points for cardiovascular risk over a 10-year period were used: a) low CVR <5%, intermediate CVR (5 to <20%) and high CVR ($\geq 20\%$).^{21,32}

The NHS questionnaire and the variables have been published in prior publications and greater details can be found in other publications.²⁷ According to that set forth in the study protocol, all of the results of the exams were informed to the user by the laboratory in charge. In cases of abnormal results, the users were advised to seek out medical assistance in public health services. In cases of extreme risk, the users were contacted directly by the partner laboratory or by the Ministry of Health, attempting to provide immediate medical care assistance.²⁸

It should also be noted that the NHS was approved by the National Ethics Commission on Research, logged under protocol number 328.159, on June 26, 2013. All individuals were consulted, their doubts clarified, and agreed to participate in this study.

Results

This study shows that 58.4% of women presented low cardiovascular risk (<5%); 32.9% intermediate GRS (5 to 19%) and 8.7% high GRS ($\geq 20\%$). The high GRS in women increased with age, from 0.1% in the 40–44-year-old group to 9.3% in the 50–54-year-old group; 10.6% in the 55–59-year-old group; 29% in the 60–64-year-old group; 29.9% in the 65–69-year-old group, and 38.4% in the 70–74-year-old group. The difference in the GRS according to years of education was nearly five-fold comparing the high level of education (12 years or more) with the low level of education (<8 years) (3.2%: 95% CI 2.4–4.4 versus 15.7%: 95% CI 13.5–18.3). Those who had health insurance presented a lower GR, 5.4% (95% CI 3.9–7.3) versus 10.2% (95% CI 8.8–11.8) of those who did not. Black women represented the largest proportion in the high-risk group ($\geq 20\%$): 14.4% (95% CI 9.7–20.9), compared to white women, 7.3 (95% CI 5.8–9.1). The self-evaluation of bad health showed the largest difference among women, and presented a gradient, considering the following extremes: women who self-evaluate themselves as having good health, 2.9% (95% CI 1.3–3.6), and very bad health, 25.6% (12.7–45.0) (Table 1).

Among men, 36.5% presented low cardiovascular risk (<5%); 41.9% presented intermediate GRS (5 to 19%); and 21.6%, high GRS ($\geq 20\%$). The high GRS in men increased with age, from 1.0% in the 40–44-year-old group; 4.9% in the 45–49-year-old group; 17.1% in the 50–54-year-old group, 44.7% in the 55–59-year-old group; 61.5% in the 60–64-year-old group; 78.2% in the 65–69-year-old group, 91.9% in the 70–74-year-old and older group. The difference in the CVR, according to the level of education, was nearly twice as high, 13.8% (12 years or more) and 29.8% (<8 years). No difference was identified in the GRS considering race and skin color,

and having health insurance. The self-evaluation of health in men also presented a gradient: very good, 11.4% (95% CI 8–15.9) and the self-evaluation of bad health, 39.1% (95% CI 28.8–50.4) (Table 2).

Figure 1 shows the proportional distribution of the Framingham model components, by risk groups, which contributed positively (greater than zero) to the total score. In the high risk among women, the indicators that most contributed to the GRS were: systolic blood pressure (97.7%), TC (91.3%), diabetes (62.8%), HDL cholesterol (60.6%) and smoking. In the high risk among men, the indicators that most contributed to the GRS were: TC (85%), systolic blood pressure (84.3%), HDL cholesterol (76.2%), smoking (39.9%) and diabetes (24.7%).

Discussion

This study is the first national population-based study to estimate the GRS for the Brazilian adult population using laboratory data. For the calculation, algorithms were employed by D'Agostino et al.²⁰ according to findings from the Framingham study. These models were estimated by mathematic functions to estimate the absolute risk of CVD in a 10-year period.²⁰ A high GRS ($\geq 20\%$) was found in nearly 8.7% of the women and nearly one fifth of the men. GRS increased with age, affecting approximately 40% of the women between 70 and 74 years of age and nearly all of the men in this age range. The risk quadrupled among women with low level of education and doubled among men. It is worth noting that there is a large concentration of individuals with GRS greater than 20% in the groups with low levels of education and older individuals. Part of this concentration may be an effect from the cohort, given that, on average, older individuals are less educated than the younger ones.³³ An important portion of the concentration of the less educated individuals in the high-risk group can be explained by the more advanced age of the group and vice-versa. Other analyses, which are not in the scope of this study, can separate the effects.

Only black women, compared to white women, represented a larger proportion in the high-risk group. What is surprising is the absence of a statistically significant race/color difference in the percentage of men with high GRS. It is likely that part of the differential potential by race has been captured by other correlated variables, such as age and level of education. In the sample, the white male population, as compared to the blacks and light-skinned blacks, show a greater concentration in older ages. Among women, the risk was higher among those that do not have health insurance and a dose-response gradient was also observed between CVR and the self-evaluation of health, reaching eight-fold higher levels between the very good and very bad evaluations, whereas among men this difference was approximately 3-fold higher. The factors that most frequently contributed to the high GRS were age, blood pressure and high cholesterol.

Various risk assessment calculations were developed to estimate the CVR according to the Framingham study findings. The current score was revised in 2008²⁰ and includes additional cardiovascular clinical parameters. Although this risk model provides an improved CVD estimate, it still faces some challenges

Table 1 – Proportional distribution of the selected variable by cardiovascular risk groups, women, NHS 2013

Variable	Less than 10%		Between 11% and 20%		Greater than 20%	
	n	%	n	%	n	%
Women	2092	58.4 (56.3;60.5)	1180	32.9 (31;35)	312	8.7 (7.6;9.9)
Age						
30–34	564	100	0	-	0	-
35–39	482	94.1 (90.2;96.5)	30	5.8 (3.4;9.8)	0	0 (0;0.3)
40–44	404	84.9 (80.2;88.6)	72	15 (11.3;19.7)	1	0.1 (0;0.9)
45–49	353	70.3 (64.8;75.3)	147	29.3 (24.3;34.8)	2	0.4 (0.1;1.6)
50–54	161	39.2 (33.3;45.5)	211	51.4 (45.2;57.6)	38	9.3 (6.3;13.7)
55–59	87	22.1 (17.1;28)	265	67.3 (61;73)	42	10.6 (7.6;14.7)
60–64	28	9.3 (6.2;13.6)	186	61.7 (54.8;68.2)	87	29 (23;35.9)
65–69	12	4.5 (2.4;8.5)	172	65.5 (58.2;72.2)	79	29.9 (23.6;37.2)
70–74	2	1.5 (0.5;4.1)	98	60.2 (50.5;69.1)	63	38.4 (29.5;48.1)
Level of education						
0–8 years	572	40.2 (37.1;43.3)	628	44.1 (41;47.2)	224	15.7 (13.5;18.3)
9 to 11	293	61.5 (55.3;67.3)	151	31.6 (26.1;37.7)	33	6.9 (4.5;10.4)
12 and over	1227	72.9 (70;75.7)	401	23.8 (21.2;26.7)	54	3.2 (2.4;4.4)
Skin color						
White	1003	58.3 (55;61.6)	591	34.4 (31.3;37.6)	125	7.3 (5.8;9.1)
Black	169	49.8 (42.7;56.9)	122	35.8 (29.4;42.7)	49	14.4 (9.7;20.9)
Light-skinned Black	891	60.1 (57.2;62.8)	457	30.8 (28.3;33.5)	135	9.1 (7.6;10.9)
Other	30	69.4 (49.1;84.2)	11	24.8 (11.4;45.7)	2	5.9 (2.2;14.8)
Region						
North	150	61.8 (58.5;65)	63	29.5 (26.5;32.6)	12	8.7 (7;10.8)
Northeast	561	54.8 (52.1;57.4)	278	32.7 (30.3;35.2)	85	12.6 (11;14.4)
Southeast	910	49.9 (46.2;53.5)	578	36.3 (32.9;39.9)	152	13.8 (11.6;16.4)
South	308	50.7 (46.3;55)	177	36.1 (32.1;40.2)	46	13.3 (10.7;16.3)
Midwest	164	54.9 (50.3;59.5)	84	33.1 (28.9;37.5)	16	12 (9.4;15.2)
Health Insurance						0 (0;0)
No	1375	56 (53.5;58.4)	830	33.8 (31.5;36.2)	251	10.2 (8.8;11.8)
Yes	717	63.6 (59.6;67.4)	350	31.1 (27.4;35)	60	5.4 (3.9;7.3)
Self-evaluation						
Very good	313	73.4 (67;78.9)	102	23.8 (18.5;30)	12	2.9 (1.3;6)
Good	1188	67.3 (64.3;70.1)	500	28.3 (25.6;31.2)	78	4.4 (3.3;5.8)
Regular	504	44.3 (40.9;47.8)	469	41.2 (37.7;44.8)	165	14.5 (12.1;17.2)
Bad	69	33.1 (26;41.2)	94	45.1 (37.4;53.1)	45	21.7 (15.9;29)
Very bad	17	39.2 (24.5;56.2)	16	35.1 (22.6;50.2)	11	25.6 (12.7;45)

Source: National Health Survey, 2013.

and underestimates the risk in women.²¹ The classification employed in this study used the Cox model and covariables, such as age, TC, HDL cholesterol, treated and untreated systolic blood pressure, antihypertensive medications, current smoking and the status of diabetes with the CVR calculation.²⁰ The authors transformed the continuous variables into logarithms to improve

the discrimination and calibration of the models and to minimize the influence of extreme observations.²⁰

The algorithms were recommended by the Brazilian Society of Cardiology in the first version of the Brazilian Guidelines for Cardiovascular Disease Prevention²¹ and add advantages in the identification of the GRS, selecting priority

Original Article

Table 2 – Proportional distribution of selected variables by cardiovascular risk groups, men, NHS 2013

Variable	Less than 10%		Between 11% and 20%		Greater than 20%	
	n	%	n	%	n	%
Men	950	36.5 (34.1;39.1)	1088	41.9 (39.4;44.4)	562	21.6 (19.7;23.6)
Age						
30–34	390	96.4 (92.9;98.2)	15	3.6 (1.8;7.1)	0	–
35–39	342	84.5 (78.9;88.7)	63	15.5 (11.3;21.1)	0	–
40–44	139	38.2 (31.8;45)	221	60.8 (53.9;67.2)	4	1 (0.4;2.4)
45–49	63	18.7 (13.9;24.6)	258	76.4 (70.2;81.7)	16	4.9 (2.7;8.5)
50–54	17	5.1 (3;8.6)	250	77.7 (71.7;82.7)	55	17.1 (12.7;22.8)
55–59	0	–	142	55.3 (47.4;62.9)	115	44.7 (37.1;52.6)
60–64	0	–	99	38.5 (31.3;46.2)	158	61.5 (53.8;68.7)
65–69	0	–	33	21.8 (15.7;29.4)	118	78.2 (70.6;84.3)
70–74	0	–	8	8.1 (4.2;15.2)	95	91.9 (84.8;95.8)
Level of education						
0–8 years	237	21.8 (19.1;24.8)	525	48.4 (44.8;51.9)	324	29.8 (26.8;33.1)
9 to 11	163	41.8 (35.1;48.8)	145	37.1 (30.7;44)	82	21.1 (16.2;27)
12 and over	550	48.9 (44.8;53.1)	418	37.2 (33.3;41.3)	155	13.8 (11.4;16.7)
Skin color						
White	408	33.5 (29.8;37.5)	532	43.7 (39.8;47.7)	277	22.8 (19.8;26.1)
Black	92	34 (26.8;42.1)	129	47.9 (39.6;56.3)	49	18.1 (12.7;25)
Light–Skinned black	441	40.5 (36.8;44.2)	415	38.2 (34.8;41.6)	233	21.4 (18.8;24.3)
Other	10	41.1 (23.1;61.9)	12	47.4 (27;68.7)	3	11.5 (4.9;24.7)
Region						
North	70	39.7 (35.7;43.7)	78	44.3 (40.3;48.3)	28	16.1 (13.4;19.2)
Northeast	274	40.2 (36.9;43.6)	283	41.6 (38.4;45)	124	18.2 (15.7;20.9)
Southeast	391	34.2 (29.6;39.2)	463	40.5 (35.8;45.4)	288	25.2 (21.6;29.3)
South	143	3.,9 (30.3;42)	170	42.9 (37.2;48.8)	84	21.2 (17.1;25.9)
Midwest	72	35.8 (30;41.9)	93	45.9 (40.1;51.8)	37	18.3 (14.4;23)
Health insurance						
No	649	34.9 (32.1;37.8)	790	42.6 (39.7;45.4)	418	22.5 (20.3;24.9)
Yes	302	40.6 (35.5;45.9)	298	40.1 (35.1;45.3)	143	19.3 (15.7;23.5)
Self-evaluation						
Very good	210	52.8 (45.7;59.8)	143	35.8 (29.5;42.7)	45	11.4 (8;15.9)
Good	566	41 (37.5;44.6)	562	40.7 (37.3;44.2)	254	18.4 (15.9;21.1)
Regular	159	22.7 (19.2;26.7)	323	46.2 (41.6;50.8)	218	31.1 (27.1;35.4)
Bad	13	13.3 (8.4;20.5)	46	47.6 (36.3;59.2)	37	39.1 (28.8;50.4)
Very bad	2	7.6 (2.2;22.7)	14	61.3 (39.1;79.7)	7	31.1 (14.7;54.2)

Source: National Health Survey, 2013.

individuals for intervention, with multiple risk factors, avoiding the unnecessary identification of people with only one isolated risk.²⁰ These estimations of global CVD support the identification of selected patients for prevention and treatment measures, making the measures cost-effective²¹ and useful for application in primary care.

The proposed algorithm is classified according to sex, increasing the risk score with increasing age, smoking habits, untreated BP and diabetes.²⁰ Among women, the algorithm increases in post-menopause age ranges and raises the risk for such factors as smoking and diabetes. Despite the use of higher scores for women, the GRS was still twice as high among men.

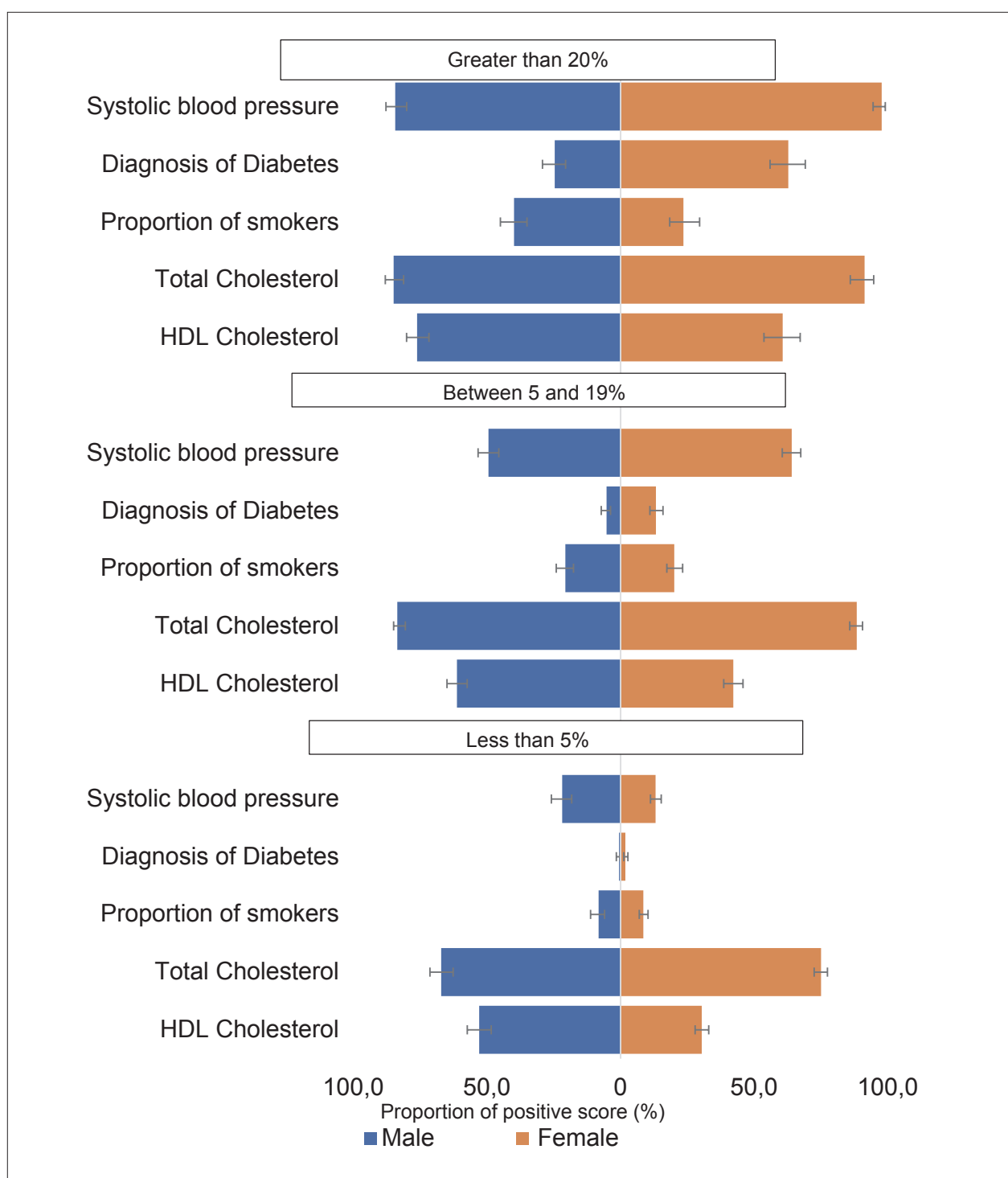


Figure 1 – Proportional distribution of the components of the Framingham model by high, intermediate, and low-risk groups, respectively, by sex, NHS 2013. Source: National Health Survey, 2013

In Brazil, some studies measured the CVR among adults and the elderly, employing the Framingham calculation,³⁴ as seen in the Bambuí cohort. Adults (n=547, 30–59 years of age) and the entire elderly population (n=1165, 60–74 years of age) were analyzed, and the CVR among the elderly was

found in 56% of the men and 21% of the women.³⁵ Another national study, which evaluated approximately 15,000 individuals who received medical care in the check-up service of the Preventive Medical Center of the Israelita Albert Einstein Hospital between 2009 and 2015, also identified

similar proportions. High CVR in women was 12.3% and in men was 40.1%.²³

The higher CVR in men reflects the presence of less healthy lifestyles, such as smoking, improper diet, alcohol consumption, infrequent search for health services, non-use of medications, which has been documented in a number of other national studies.³⁵⁻³⁷

The increase in risk with age has been attributed to aging, increase in BP, which can affect 60% of the elderly, according to data from the NHS.³¹ The explanations would be the inherent changes that come with aging, including hardening of the arteries, greater peripheral vascular resistance and comorbidities among the elderly.^{21,38-40}

In the case of women, the rise in GRS in the post-menopause age range results from the loss of the hormone prevention effect in this stage of life. The increase in hypertension in women has been described by the growth of central obesity with the increase in age.^{31,40}

A wide range of studies have also indicated that detection, treatment and control of high blood pressure are crucial to reduce the incidence of cardiovascular events.⁴¹ The Framingham study pointed out that high blood pressure increases the chance of cardiovascular events, which is even higher in the absence of treatment.

The GRS increases with smoking,^{9,21} which is highly documented in the literature, including in the Framingham studies.^{20,22} The cardiovascular guidelines highly recommend that the patient stop smoking as a priority measure in the secondary prevention of cardiovascular diseases and other untreated cardiovascular diseases.²¹

Individuals who self-perceive their own health as bad or very bad presented CVR almost eight times higher among women and three times higher among men. The self-evaluation of health constitutes an excellent predictor of mortality and severe events, both in international⁴² and in national events.⁴³ This is due to the individual's own risk perception, brought about by the symptoms, lifestyle changes due to the disease, greater frequency of visits to healthcare services, doctor's appointments, use of medications and the limitation of daily activities.⁴³

This study highlights a greater GRS in individuals with low level of education, which has been identified in other international⁴⁴ and national studies, such as ELSA-Brasil.⁴⁵ The socioeconomic adversities have a strong association with morbidity and mortality through CVD,⁴⁶ subclinical atherosclerosis, worse manifestations such as metabolic indicators⁴⁷ a consequence of socioeconomic disadvantages, adversities in childhood,⁴⁵ worse access to healthcare services, and health promotion and prevention practices.⁴⁸ In this sense, the results reinforce the importance of taking into consideration socioeconomic variables in the planning of public policies for CVD prevention.

The limitations of this study include the use of algorithms from the study conducted by Framingham. Since Framingham's studies were conducted many decades ago, CVD risks may have changed, and the study findings do not necessarily reflect what occurs in other populations as regards ethnic and cultural differences and others.²² Another limitation consists of the non-inclusion of other risk factors in the calculation, such as diet, body

weight and physical exercise; clinical conditions; and the use of medication to control cholesterol.^{21,24} As this is a cross-sectional design, it was also impossible to follow up on future outcomes, as it occurs in longitudinal studies. The laboratorial base used in this study presented sample losses, which were minimized by the weighting used; however, the bias may not have been corrected, thus making the estimations subject to review in future studies.

In Brazil, the longitudinal study of adult health (ELSA-Brasil), using different calculations, calculated CVR over a 10-year period in 6.9% and 7.6%.⁴² These different classifications highlight the need, in future studies, to explore other CVR classifications, including in the scores of other risk factors, such as: abdominal obesity, improper diet, and a lack of physical activity.^{21,49}

The CVR calculations have been widely used to identify at-risk populations and those that should be the target of health promotion, prevention and treatment measures. The protocols can vary according to the consensus of the specialists, but in all of these, a healthy diet is recommended, including the consumption of fruits and vegetables; reduction of salt, fat and sugar; stopping smoking, doctor's advice or medical treatment, as needed; reduction in alcohol consumption; physical exercise; approaches toward obesity and overweight; non-drug treatments combined with medications for patients with hypertension, diabetes, high cholesterol; and other changes, depending on specific characteristics.²¹ These approaches should be monitored, defining the therapeutic target and monitoring the evolution.

Conclusion

This study identified the GRS over a 10-year period in the Brazilian adult population, with an estimated risk of 8.7% among women and 21.6% among men. Individuals with a high CVR require more aggressive changes in their risk factors.²¹ The GRS can still be used to monitor the progress of patients in treatment and improve their risk scores. These data highlight the need for advances in preventive actions, primarily guiding population strategies in the search for high-risk populations, which, in general, include medication and non-medication approaches.

Authors' contributions

Conception and design of research, Analysis and interpretation data and Critical revision of the manuscript for content: Malta DC, Pinheiro PC, Teixeira RA, Machado IE, Santos FM, Ribeiro AL; Obtaining data and Writing the manuscript: Malta DC, Pinheiro PC; Statistical analysis: Pinheiro PC, Teixeira RA; Obtaining financing: Malta DC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

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“Know the Enemy and Know Yourself”. Cardiovascular Risk in the National Health Survey

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Short Editorial related to the article: Cardiovascular Risk Estimates in Ten Years in the Brazilian Population, a Population-Based Study

The Art of War by Sun Tzu¹ is a masterpiece about military strategy published around 2,500 years ago. In his work, Tzu states: “If you know the enemy and know yourself, you need not fear the result of a hundred battles.” Although we are not army generals, teachings from Tzu may be proven useful in cardiovascular science as well. They reinforce the need for understanding the current picture of cardiovascular epidemiology in our society and how it evolves, as a primary weapon to determine how resources and efforts may be more efficiently applied.

Cardiovascular diseases remain a major cause of death and disability worldwide. Although research in the past decades have substantially improved our knowledge about the main drivers of cardiovascular disease epidemiology, the high rates of cardiovascular morbimortality yields a very heterogeneous picture around the globe.² In our country, for example, in the past few decades we have experienced a sharp decline in smoking in all Brazilian states.³ However, we also observed raising trends for other risk factors such as diabetes⁴ and other obesity-related metabolic changes,⁵ as well as population aging, producing mixed impacts on cardiovascular morbimortality rates.

In articles recently published in *Arquivos Brasileiros de Cardiologia*, visibility has been given to cardiovascular risk in special populations in our country. Silva et al.⁶ have studied 71 individuals living with HIV (a population with high cardiovascular risk compared to the general population⁷) in Minas Gerais. Participants in that study had a mean age of 47.2 years, and 53% were men. They found that more than one-fourth of those participants had >20% probability of

cardiovascular events in 10 years. Oliveira et al.⁸ studied 11 consecutive male patients with psoriasis (an inflammatory disorder also associated with increased cardiovascular risk⁹) and 33 age-matched controls and found significantly higher total cholesterol, LDL-cholesterol and C-reactive protein levels and a trend towards higher frequencies of smoking and hypertension diagnosis in individuals with psoriasis compared to controls.

In the current issue of *Arquivos*, Malta et al.¹⁰ analyzed data from the National Health Survey conducted in 2013, with subsequent laboratory assessments conducted in 2014 and 2015. It is important to state that this is a necessary contribution to the field. Firstly, the adopted methodology shows the “big picture” of cardiovascular risk in our country, with a large and representative sample. Secondly, the authors present detailed information about Framingham risk score distributions according to sociodemographic characteristics in our country, using adequate statistical tools to account for sampling biases. Finally, the addition of blood pressure and laboratory measurements for a subsample of the National Health Survey substantially reduces the impact of underdiagnosis in the results. Among their main results, the authors estimate that 5.8% of women and 21.6% of men in our country have high (>20%) risk for cardiovascular events in 10 years.

Further advance is surely needed in this field. One important point is that the extent to which the classical Framingham risk score is appropriate for identifying risk for the Brazilian population is not clear. Interestingly, the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk¹¹ identified the need for race-specific scoring criteria. Its authors describe different equations for White and African Americans and recognize the limitations of applying the same calculations for other ethnic groups. It may be true that our estimates of cardiovascular risk will be even more accurate as more “native” information becomes available from long-term cohort studies in Brazil.¹² Advancing in cardiovascular epidemiology research will allow us to know the enemy, to know ourselves and to win more battles.

Keywords

Cardiovascular Diseases/mortality; Epidemiology; Risk Factors; Obesity; Aging.

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Exercise-Based Cardiac Rehabilitation Has a Strong Relationship with Mean Platelet Volume Reduction

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Abstract

Background: Mean platelet volume (MPV), which is a simple measure of platelet activation, has recently become an interesting topic in cardiovascular research. Exercise-based cardiac rehabilitation (CR) is a comprehensive intervention that decreases mortality-morbidity in patients with coronary artery disease (CAD). Studies on the effects of exercise on platelet activation have yielded conflicting results.

Objective: The purpose of this study was to determine the effect of an exercise-based CR programs on MPV in patients with stable CAD.

Methods: The sample was composed of 300 consecutive stable CAD patients. The patients were divided into two groups: CR group (n = 97) and non-CR group (n = 203). Blood analysis was performed. Point-Biserial correlation measures were performed to show correlation between MPV change and CR. A p value of <0.05 was considered statistically significant.

Results: The decrease in MPV was greater in the CR group than in the non-CR group [(-1.10(-1.40-(-0.90)) vs. (-0.10(-2.00-0.00)); p< 0.001]. Δ MPV had a positive correlation with Δ neutrophil (r = 0.326, p < 0.001), Δ TG (r = 0.439, p < 0.001), Δ LDL-c (r = 0.478, p < 0.001), Δ WBC (r = 0.412, p < 0.001), and Δ CRP (r = 0.572, p < 0.001). A significant correlation was found between Δ MPV% and CR (r=0.750, p<0.001).

Conclusions: We were able to show that exercise-based CR has a strong relationship with MPV reduction in patients with CAD. We consider that decreased platelet activation with exercise-based CR might play an important role in reducing thrombotic risk in patients with stable CAD. (Arq Bras Cardiol. 2021; 116(3):434-440)

Keywords: Cardiac, Rehabilitation; Exercise; Physical, Activity; Mean Platelet Volume; Blood Platelets; Coronary artery Disease; Echocardiography/methods

Introduction

Cardiovascular (CV) disease is one of the leading causes of mortality and disability and remains a major concern despite improved clinical outcomes with evidence-based treatment.^{1,2} Platelets are essential for primary hemostasis and repair of the endothelium, but they also play a key role in the pathogenesis of atherosclerosis and arterial thrombosis.¹ Platelet activation is associated with CV events.³ Monitoring the function of platelets may help to evaluate the prognosis of patients with coronary artery disease (CAD).⁴

However, because platelet function testing is a time-consuming, costly, and technically challenging process, it is not widely used.⁴ Compared with smaller platelets, larger platelets contain dense granules, express more adhesion receptors, and induce higher thrombotic activity, which can reflect the degree

of platelet activation.⁵ Mean platelet volume (MPV) is a major parameter of platelet size that has been proposed as an indicator of platelet reactivity and is routinely determined by complete count analyzers at a relatively low cost.⁶ Increased MPV levels have been reported to be associated with CAD, myocardial infarction, peripheral arterial disease, cerebrovascular disease, and poor outcome.⁷

Exercise-based cardiac rehabilitation (CR) is a comprehensive intervention that includes medically supervised exercise training, risk factor management, patient education, and psychosocial counseling.⁸ CR has been proven effective in improving exertional ischemic symptoms, exercise tolerance, and coronary risk factors in patients with CAD. Also, it was shown to also reduce all-cause and CV mortality in 20% to 32% among patients with CAD.⁹

Studies on the effects of exercise on platelet activation have yielded conflicting results.² The purpose of this study was to determine the effect of an exercise-based CR program on MPV in patients with stable CAD.

Methods

Study population

Sample size was determined with 80% power and 5% margin of error after preliminary evaluation of 5-10 cases.

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The study included 300 consecutive outpatients who had undergone coronary angiography (CAG) in the previous six months due to stable angina pectoris and >50% stenosis detected in at least one coronary artery, or had a history of percutaneous coronary intervention (PCI)/coronary artery bypass graft (CABG) surgery, and had been referred to a Phase-III CR program. The non-CR group was composed of 97 patients who did not agree to participate in the CR program. Patients with immunologic or inflammatory diseases, hematological diseases, sepsis, active local or systemic infections, chronic renal disease ($\text{eGFR} < 30 \text{ mL/min/1.73 m}^2$), age ≤ 18 and > 80 , left ventricular ejection fraction (LVEF) $< 40\%$, or with history of malignancy were excluded.

Patients' medical treatments were optimized before the participation, and none of them had changes in medication during the study.

Blood analysis was performed in patients included in the CR group one day before the start of the program and one day after the end of the program (which lasted six weeks) after a 12-hour fasting. On the other hand, in patients who were not included in the CR program, blood analysis was performed upon their inclusion in the study and six weeks later, after a 12-hour fasting. All samples were obtained in standardized dipotassium ethylenediaminetetraacetic acid (EDTA) tubes. The blood counts were measured using an automated hematology analyzer Advia 2120 (Siemens). Fasting blood glucose, low-density lipoprotein cholesterol (LDL-c), triglycerides (TG), high-density lipoprotein cholesterol (HDL-c), white blood cell (WBC), C-reactive protein (CRP), creatinine, and hemoglobin values were measured. Body mass index (BMI) was calculated as weight (kg)/height (m^2).

Calculation of the Gensini score was initiated by giving a severity score to each coronary stenosis: 1 point for $\leq 25\%$ narrowing, 2 points for 26 to 50% narrowing, 4 points for 51 to 75% narrowing, 8 points for 76 to 90% narrowing, 16 points for 91 to 99% narrowing, and 32 points for total occlusion. Thereafter, each lesion score was multiplied by a factor that takes into account the importance of the lesion's position in the coronary circulation (5 for the left main coronary artery, 2.5 for the proximal segment of the left anterior descending coronary artery, 2.5 for the proximal segment of the circumflex artery, 1.5 for the mid-segment of the left anterior descending coronary artery, 1.0 for the right coronary artery, the distal segment of the left anterior descending coronary artery, the poster lateral artery, and the obtuse marginal artery, and 0.5 for other segments). Finally, the Gensini score was calculated by summation of the individual coronary segment scores.¹⁰

Echocardiographic measurements were taken according to the American Society of Echocardiography guidelines. The left ventricle (LV) end-diastolic volume (EDV) and end-systolic volume (ESV) were calculated from the apical two- and four-chamber views using the modified Simpson' method. The LVEF was calculated as $\text{LVEF} = (\text{EDV} - \text{ESV}) / \text{EDV} \times 100$.

This study was performed in accordance with the Declaration of Helsinki and with the approval by the local ethics board.

CR program

A step incremental cycle ergometer test was applied before the CR program in patients in the CR group, so as to determine their exercise capacity. During the test, the aim was to reach the expected maximum heart rate according to age ($220 - \text{age}$). The indications for terminating the exercise testing were: ST-segment deviation, moderate to severe angina, drop in systolic blood pressure $> 10 \text{ mmHg}$ (persistently below baseline) despite an increase in workload, hypertensive response (systolic blood pressure $> 250 \text{ mmHg}$ and/or diastolic blood pressure $> 115 \text{ mmHg}$), central nervous system symptoms (e.g., ataxia, dizziness, or near syncope), fatigue, shortness of breath, wheezing, leg cramps, or claudication. After a two-minute resting period, the workload was increased by 25W every two minutes. Heart rate and blood pressure were measured during the whole test. The maximum workload was determined as the maximal exercise capacity.

The CR program was performed with the supervision of a multidisciplinary team, including a cardiologist, an experienced physical therapist as a coordinator, and a physical therapy and rehabilitation specialist as the medical director. The rehabilitation program was performed in the CR center of our cardiology and cardiovascular surgery hospital.

The CR program consists of aerobic exercise training and relaxation exercises. Based on the result of the exercise testing, exercise prescription was scheduled individually. Patients remained in the program five days a week, for a total of six weeks. All patients in the CR group completed the program. Each session lasted 30 minutes, including the five-minute warm-up and the final five-minute cool-down. The aerobic exercise intensity was prescribed according to the individual's exercise capacity. The intensity began at 40-50% of maximal heart rate reserve and gradually increased to 70-85% of maximal heart rate reserve. Heart rate reserve was evaluated by the Karvonen Formula ($\text{HR}_{\text{train}} = (\text{HR}_{\text{max}} - \text{HR}_{\text{rest}}) \times \text{ExerciseIntensity} + \text{HR}_{\text{rest}}$).¹¹ HR_{train} being the heart rate during the aerobic exercise, HR_{max} the maximum heart rate reached thorough the cycle ergometer test, and HR_{rest} the heart rate at rest. The Borg Scale of Rate of Perceived Exertion (RPE) was used, and patients exercised at an RPE of 13-15. Patients were continuously monitored by electrocardiography (ECG) with a 1-channel ECG transmitter (Custo med, Ottobrunn, Germany), and systolic/diastolic blood pressure measurements were performed automatically every five minutes via a software system (Custo med, Ottobrunn, Germany). During the study, patients were also directed to a psychologist, a dietitian, and a smoking cessation clinic.

Statistical analysis

Statistical analyses were carried out using the SPSS statistical software (version 21.0, SPSS, Chicago, IL, USA). Continuous variables are presented as mean and standard deviation. Categorical variables are presented as numbers and percentages. The variables were compared using the two-tailed student t test for continuous variables of normal distribution or the Mann-Whitney U test for continuous variables of non-normal distribution. The Kolmogorov-Smirnov test was applied to verify the normality of the distribution

of continuous variables. The chi-square test was used for categorical variables. The related test or Wilcoxon signed-rank test was used to compare variables before and after therapy. Spearman's correlation analysis was performed to examine the relationship between continuous variables. Point-Biserial correlation measures were performed to show the correlation between MPV changes and the CR. A p-value of <0.05 was defined as statistically significant.

Results

The study population (300 patients) was divided into two groups according to their ingress in the CR program. Two hundred three patients participated in the CR program (CR group), and 97 patients did not (non-CR group). Demographic and clinical characteristics, as well as laboratory findings of the population, as listed in Table 1. History of acute coronary syndrome, CABG, and PCI was similar in both groups (Table 1).

Table 1 – Clinical and laboratory characteristics of CR and non-CR groups

Variables	non-CR group (n=97)	CR group (n=203)	p value
Age (year)	57.9±7.4	56.2±7.8	0.072
Gender (Male %)	74(76.3%)	159(78.3%)	0.399
Hypertension (n, %)	82(84.5%)	184(90.6%)	0.088
Diabetes mellitus (n, %)	20(20.6%)	55(27.1%)	0.142
Current smoker (n, %)	11(11.3%)	27(13.3%)	0.391
BMI (kg/m ²)	28.2±3.1	28.3±3.9	0.885
PCI history (n, %)	61(62.9%)	117(57.6%)	0.230
ACS history (n, %)	28(28.9%)	50(24.6%)	0.259
CABG history (n, %)	19(19.6%)	37(18.2%)	0.446
LVEF %	57.1±5.3	58.3±5.6	0.086
CAD severity			
1 vessel	35(36.1%)	89(44.1%)	
2 vessels	58(59.8%)	98(48.5%)	
>2 vessels	4(4.1%)	15(7.4%)	0.155
Gensini Score	54.1±28	50.1±28.2	0.266
ASA (n, %)	95(97.9%)	200(98.5%)	0.745
P2Y12 inhibitors (n, %)	60(61.5%)	115(56.6%)	0.493
Beta-blockers (n, %)	82(84.5%)	158(77.8%)	0.113
Calcium-channel-blockers (n, %)	42(43.3%)	91(44.8%)	0.451
RAAS inhibitors (n, %)	80(82.5%)	165(81.3%)	0.469
Statin (n, %)	92(94.8%)	197(97.5%)	0.377
Fasting plasma glucose (pre) (mg/dL)	102.6±27.1	106.2±33.7	0.307
Creatinine (pre) (mg/dl)	0.9±0.21	0.87±0.21	0.374
Hemoglobin (pre) (g/dL)	13.4±1.02	13.6±1.07	0.135
MPV (pre)	8.7±0.98	9.1±1.02	0.010
MPV (post)	8.6±0.98	7.9±0.82	<0.001
ΔMPV*	-0.10 (-2.00-0.00)	-1.10(-1.40-[-0.90])	<0.001*
ΔMPV %*	-1.15 (-2.37-0.00)	-12.63(-14.46-[-10.11])	<0.001*
ΔLDL-c (mg/dL)*	-2.00 (-1.00-0.00)	-20.00 (-36.00-[-10.00])	<0.001*
ΔTG (mg/dL)*	-9.00 (-10.50-[-1.00])	-21.00 (-49.00-[-10.00])	<0.001*
ΔHDL-c (mg/dL)*	1.00 (0.00-1.00)	4.00 (3.00-6.00)	<0.001*
ΔWBC (10 ³ /μ ³)*	0.10 (-0.25-0.30)	-0.70(-1.20-[-0.35])	<0.001*
ΔNeutrophil (10 ³ /μ ³)*	-0.10 (-0.50-0.03)	-0.80 (-1.50-[-0.39])	<0.001*
ΔCRP (mg/dL)*	-0.10 (-0.10-0.10)	-0.80 (-1.80-[-0.40])	<0.001*

Data are presented as mean ± standard deviation or number of patients and percentage of patients. CR: cardiac rehabilitation; Δ: delta; BMI: body mass index; PCI: percutaneous coronary intervention; ACS: acute coronary syndrome; CABG: coronary artery bypass graft; LVEF: left ventricular ejection fraction; CAD: coronary artery disease; ASA: acetylsalicylic acid; RAAS: rennin-angiotensin-aldosterone; MPV: mean platelet volume; LDL: low density lipoprotein; TG: Triglycerides; HDL: high density lipoprotein; WBC: white blood cell; CRP: C-reactive protein; pre: before CR. *Comparison by Mann-Whitney U test at $p<0.05$. Values were described as medians with inter-quartile range (25th and 75th percentile).

Original Article

The decrease in MPV was greater in the CR group than in the non-CR group [((-1.10(-1.40-(-0.90)) vs. (-0.10 (-2.00-0.00)) vs.; $p < 0.001$, Table 1]. The correlation between Δ MPV and variables is shown in Table 2. As shown in Figure 1, the Δ MPV had a strong positive correlation with CR ($r = 0.750$, $p < 0.001$).

Discussion

This study showed that exercise-based CR has a strong relationship with MPV reduction in patients with CAD.

Studies on the effect of exercise on platelet activation have yielded conflicting results so far. In agreement with our study, Yazıcı et al.⁷ reported that a lifestyle change that includes at least

Table 2 – Correlation between Δ MPV and variables

	Δ MPV	
	r	p value
Δ neutrophil	0.326	<0.001
Δ LDL-c	0.478	<0.001
Δ WBC	0.412	<0.001
Δ CRP	0.572	<0.001
Δ TG	0.439	<0.001
LVEF	-0.133	0.021
hemoglobin (pre)	-0.139	0.019
fasting plasma glucose (pre)	-0.129	0.026
Δ HDL-c	-0.537	<0.001
CR	0.750	<0.001
age	0.034	0.563
BMI	-0.022	0.727

Δ : delta; MPV: mean platelet volume; LDL: low density lipoprotein; TG: Triglycerides; LVEF: left ventricular ejection fraction; HDL: high density lipoprotein; WBC: white blood cell; CRP: C-reactive protein; CR: cardiac rehabilitation; BMI: body mass index; pre: before CR.

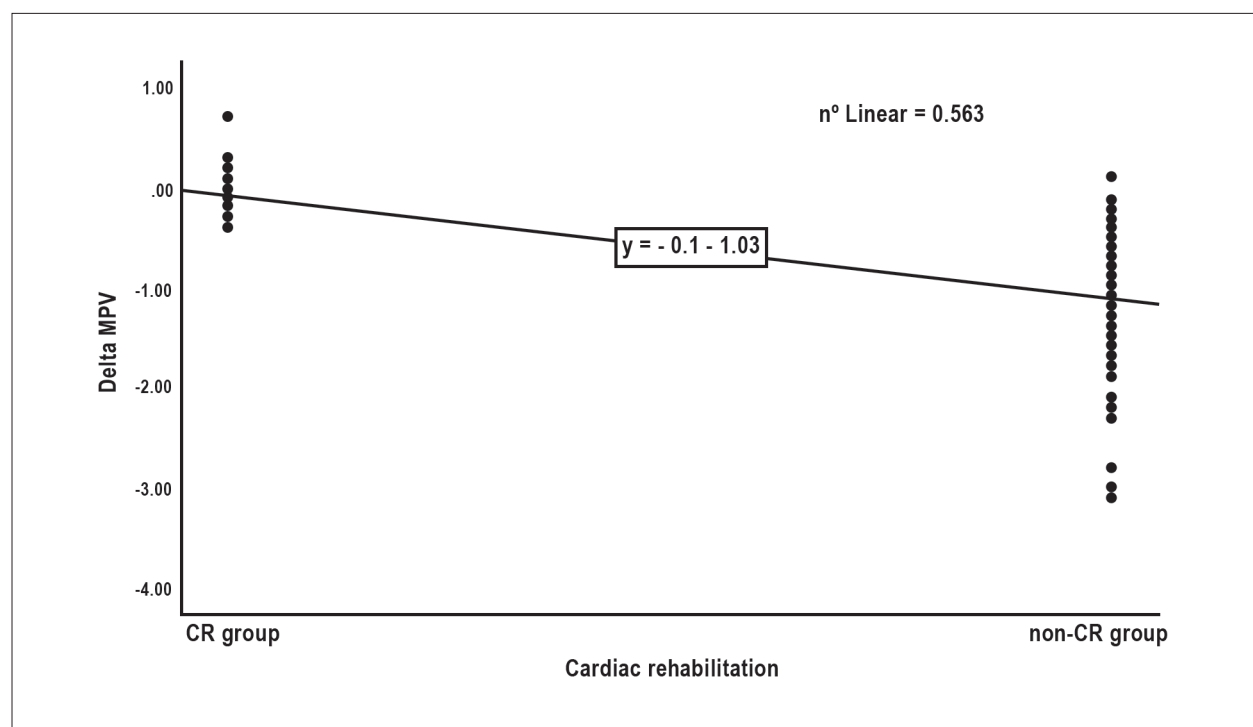


Figure 1 - Correlation of Δ MPV with CR.

180 minutes/week of moderate-intensity physical activities decreased MPV in pre-hypertensive patients. Also, Rauramaa et al.¹² showed that low to moderate intensity exercise training was associated with diminished platelet aggregation. Contrary to these results, it was shown that exercise stress test increased MPV in patients with CAD.^{11,13} Also, it has been shown that graded resistance exercises increase MPV.^{12,14}

Exercise training can bring beneficial effects on platelets via different mechanisms. With exercise training, the pulsatile flow in the aorta increases, and this might induce an acute release and upregulation of nitric oxide (NO), which is a potent mediator of antiplatelet effects and suppression of platelet reactivity.^{7,15} It is known that CR increases HDL cholesterol, which can stimulate platelet production and thereby decrease platelet activation.⁹ In our study, Δ HDL-cholesterol was found to be independently correlated with a decrease in MPV.

MPV has been recognized as an inflammatory marker in cardiovascular, cerebrovascular, rheumatologic, and gastroenterological diseases.¹⁶ Recently, it was shown that the presence of activated megakaryocytes in bone marrow correlates with increased circulating levels of IL-6 in patients with atherosclerosis.¹⁷ Previous research provided evidence that a physically active lifestyle is associated with lower whole-body inflammatory biomarkers, and the anti-inflammatory actions of chronic exercise training are evident after as little as 2 to 12 weeks of supervised exercise training.¹⁸ In our study, we demonstrated that Δ CRP was one of the independent predictors of Δ MPV. Reduction in MPV after CR might be explained by the anti-inflammatory effect of exercise-based CR programs.

The contradictions in the results of studies can be explained by various aspects of exercise affecting platelet functions such as different exercise intensity, duration, and various fitness levels of the subjects.⁷ Acute intense exercise is proven to increase plasma pro-inflammatory cytokines.¹⁸ MPV can reflect the changes in platelet stimulation and the rate of platelet production level.¹³ An increase in MPV after exercise may be attributed to the fresh release of young large platelets, particularly from the splenic pool, into the circulation.⁷ In this study, we implemented the CR program five days per week for a total of six weeks with a gradually increasing density, according to the individual's exercise capacity.

Atherosclerosis itself can stimulate bone marrow megakaryocytes, which was shown to be associated with acute coronary syndrome, by causing circulating platelet consumption during atherogenesis.¹⁷⁻¹⁹ One of the mechanisms of exercise-based CR potentially involved in the reduction of infarction and re-infarction may be related with reduction of MPV.^{9,20}

Reticulated platelets are larger and possibly more active than non-reticulated platelets.¹ Moreover, reticulated or large platelets exhibit increased reactivity despite antiplatelet therapy.^{21,22} Since it has been shown that high MPV is an independent risk factor for future myocardial infarction (MI) and recurrent MI, being associated with acute coronary syndrome or cardiovascular risk factors,^{1,19,23} the questioning on how to decrease MPV has already been raised.^{17,23} Although it was previously shown that statin treatment decreases MPV,²¹ in our study most of the patients were already on statins, so we showed the additive effect of CR on MPV reduction.

Study limitations

The present study has some limitations. First, we evaluated MPV only once and did not assess changes in it over time. Second, some anti-platelet drugs might affect platelet size.

Conclusion

This study showed that exercise-based CR has a strong relationship with MPV reduction in patients with CAD. We consider that decreased platelet activation with exercise-based CR might play an important role in reducing thrombotic risk in patients with stable CAD.

Author contributions

Conception and design of the research and Data acquisition: Durmuş I, Kalaycıoğlu E, Şahin HB; Analysis and interpretation of the data and Statistical analysis: Çetin M; Writing of the manuscript: Şahin HB; Critical revision of the manuscript for intellectual content: Durmuş I, Kalaycıoğlu E, Çetin M, Kırış T.

Potential Conflict of Interest

The authors report no conflict of interest concerning the materials and methods used in this study or the findings specified in this paper.

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There was no external funding source for this study.

Study Association

This study is not associated with any thesis or dissertation.

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Reduction in Platelet Activation: A Potential Mechanistic Link between Regular Exercise and Its Benefits for Coronary Artery Disease

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Short Editorial related to the article: *Exercise-Based Cardiac Rehabilitation Has a Strong Relationship with Mean Platelet Volume Reduction*

Exercise-based cardiac rehabilitation (CR) leads to significant reductions in mortality and risk for adverse cardiovascular events in coronary artery disease (CAD) patients.^{1,2} As a result, exercise-based CR is currently a Class 1A intervention for secondary prevention in CAD.³ However, despite considerable research efforts in the past several decades, the multidimensional mechanisms associated with the cardioprotective effects of regular exercise are still not fully elucidated.⁴

On the other hand, increased platelet activity has been increasingly recognized as a key player in the pathogenesis and progression of atherosclerosis. Through the release of cytokines and chemokines, activated platelets mediate the recruitment of leukocytes to the vascular endothelium, favoring not only plaque rupture and thrombosis, but also contributing to the early steps of atherosclerosis and the later stages of atheroprotection.⁵

Therefore, special interest has been raised regarding the role of exercise in platelet function, and conflicting results have been observed. While acute bouts of strenuous exercise seem to enhance platelet activation, and, therefore, increase the risk of thrombotic events, engaging in regular exercise has been shown to decrease platelet adhesion and aggregation, possibly contributing to the reduced atherothrombotic risk observed in physically active individuals.^{6,7}

To shed light on this topic, in the current issue of *Arquivos Brasileiros de Cardiologia*, Durmuş et al.⁸ report the effects of an exercise-based CR program on platelet activation in stable CAD patients. Mean platelet volume (MPV) was assessed at baseline and after six weeks, and pre- and post-assessment values were compared according to participation in the CR

program. The authors found that, while non-participants exhibited a non-significant MPV reduction (8.7 vs. 8.6 fL), a 13% reduction in MPV was observed in participants that completed the CR program (9.1 vs. 7.9 fL) ($p < 0.01$). Moreover, a strong positive correlation was observed between MPV variation and CR participation ($r = 0.75$). Therefore, the authors concluded that this decrease in MPV seen with CR participation might play an important role in reducing thrombotic risk in patients with stable CAD.

These significant results observed by Durmuş et al.⁸ however, require a note of caution. Platelet size, when measured as MPV, has been shown to be a marker of platelet function and has been positively associated with platelet activity indicators.⁹ Therefore, MPV is considered a valuable tool for the assessment of platelet activation. Yet, the analysis and interpretation of MPV is not straightforward. A number of pre-analytical and analytical variables, including the time between blood collection and analysis and specimen storage temperature, are known to significantly affect MPV measurements, and, as such, they represent important drawbacks when using MPV as an indirect measurement of platelet activity.¹⁰ Therefore, further studies using standardized and more reliable platelet activation markers should be undertaken to overcome these methodological issues and confirm the reported results.

In conclusion, the study conducted by Durmuş et al.⁸ opens a new avenue for future research aiming to expand our understanding on the effect of regular exercise on platelet functional behavior and the potential mechanism of exercise-induced protection in CAD patients who engage in CR programs.

Keywords

Coronary Artery Disease; Cardiovascular Diseases; Exercise; Physical Activity; Rehabilitation; Blood Platelets.

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Effects of Anti-TNF alpha Therapy on Blood Pressure in Resistant Hypertensive Subjects: A Randomized, Double-Blind, Placebo-Controlled Pilot Study

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Abstract

Background: The cytokine tumor necrosis factor-alpha (TNF- α) is elevated in resistant hypertension (RH), but the effects of a TNF- α inhibitor in this population is unknown.

Objective: The aim of this trial was to evaluate whether a single dose of infliximab controlled by placebo acutely reduces blood pressure (BP) in RH subjects.

Methods: A double-blind, placebo-controlled, crossover trial was conducted, and randomized RH subjects received either infliximab or placebo. The primary endpoint was the change in mean BP levels relative to the baseline immediately after the infusion obtained by continuously beat-to-beat non-invasive hemodynamic assessment. Secondary endpoints included changes in office, ambulatory and central BP measurements; endothelial function; and inflammatory biomarkers after 7 days. The level of significance accepted was $\alpha=0.05$.

Results: Ten RH subjects were enrolled. The primary endpoint analysis showed an acute decrease in mean BP values (mean of differences $\pm$ standard deviation = -6.3 ± 7.2 mmHg, $p=0.02$) from baseline, after the application of infliximab compared with placebo. Diastolic BP levels (-4.9 ± 5.5 mmHg, $p=0.02$), but not systolic BP levels (-9.4 ± 19.7 mmHg, $p=0.16$), lowered after infliximab infusion. No further significant differences were identified in either the other hemodynamic parameters or in secondary endpoints, except for TNF- α levels, which increased continuously after infliximab infusion. No adverse events were reported during the protocol.

Conclusions: A single-dose of infliximab decreased the mean and diastolic BP levels immediately after its infusion, when compared to the placebo in RH. The anti-TNF- α therapy was found to be safe and well-tolerated. The results of this proof-of-concept are hypothesis-generating and need to be further investigated. (Arq Bras Cardiol. 2021; 116(3):443-451)

Keywords: Hypertension; Blood Pressure; Infliximab/therapeutic use; Randomized Controlled Trial; Inflammation.

Introduction

Low-grade systemic inflammation has proven to be an underlying factor of the pathophysiology of resistant hypertension (RH) due to the lack of blood pressure (BP) control, along with coexisting conditions, such as obesity, type 2 diabetes (T2D), and metabolic syndrome. Recently, our research group has explored the role of inflammatory cytokines in this high-risk population. An elevated inflammatory score, including, among others, the proinflammatory cytokine tumor necrosis factor-alpha (TNF- α), was proposed in obese resistant subjects, when compared to controlled obese hypertensive subjects.¹ In addition, higher levels of TNF- α

have been associated with vascular damage in these RH subjects.²

While the recommendation for TNF- α inhibitor use is well established for treating some autoimmune diseases, experimental and clinical studies have demonstrated its effective use for cardiovascular (CV) system-related parameters, such as in preventing hypertension³ and reducing target organ damage (TOD).^{4,5} In fact, infliximab has revealed CV benefits as a TNF- α -neutralizing agent able to reduce systolic BP (SBP) levels and cardiac remodeling in spontaneously hypertensive rats.⁶

Since the inflammatory process is part of RH and TNF- α is implicated in CV derangements, the purpose of this proof-of-concept pilot trial was to evaluate whether a single dose of the TNF- α inhibitor, infliximab, controlled by placebo reduces BP levels in RH subjects.

Methods

Trial design

With the use of a randomized, double-blind, placebo-controlled interventional crossover design, this study explored

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the acute effects of infliximab, a TNF- α inhibitor, and its comparator placebo saline solution, as an add-on therapy to standard treatment in the population with RH. A blocked randomization scheme was created using a computer-generated code. RH subjects were randomly assigned upon enrollment to receive either (1) placebo infusion followed by infliximab infusion after a 40-day period of washout or (2) infliximab followed by placebo after a 40-day period of washout. An unblinded pharmacist distributed the study volunteers and remained with the treatment codes until study closure. The nurse who prepared the infusions was also not blinded. Both were not involved in data collection, analysis, or interpretation. A masked physician enrolled subjects into the study. Participants, evaluator physician, and the researchers assessing outcomes remained blinded after assignment to interventions.

This pilot trial was an investigator-initiated study, designed by the investigators, and no support from a commercial entity was provided. All authors certified the completeness and accuracy of the data and analyses, as well as for the adherence of the trial to the protocol.

The present study was approved by the local Research Ethic Committee (approval number 710.449, CAAE 30811214.9.0000.5404, from the School of Medical Sciences of University of Campinas-FCM/UNICAMP, Brazil) and registered in clinicaltrials.gov (NCT02743390). It was conducted in accordance with ethical principles for medical research involving human subjects established by the World Medical Association (Declaration of Helsinki), and all participants provided informed written consent before enrolling in the study. The recommendations of the Consolidated Standards of Reporting Trials (CONSORT) statement were also followed.

Population

Subjects with confirmed diagnosis of RH were recruited from a prescreened population of the Specialized Outpatient Clinic in RH at the University of Campinas (UNICAMP, Campinas, Brazil). RH was defined according to American Heart Association Statement.⁷ A precise diagnosis of RH with a 6-month clinical follow-up was performed to screen and exclude secondary causes of hypertension [renal artery stenosis (US-Doppler), pheochromocytoma (urinary metanephrines and computed tomography), primary hyperaldosteronism (aldosterone renin ratio >20 ng dl⁻¹ per ng ml⁻¹ h⁻¹), cushing syndrome (cortisol and ACTH levels), obstructive sleep apnea (classified as “high risk” at Berlin questionnaire)], and pseudo resistance (ambulatory BP monitoring (ABPM) and pill count to exclude white-coat hypertension and medication nonadherence, respectively).

Exclusion criteria were symptomatic ischemic heart disease, impaired renal function, liver disease, history of stroke, myocardial infarction and peripheral vascular diseases, type I diabetes, pregnant women, smoking, autoimmune diseases, or those who presented a contraindication to infliximab use. Non-eligible patients also consisted of those with a positive or inactive (latent) skin test for tuberculosis or with an abnormal posteroanterior chest radiography (chest X-ray) – evaluated by radiology and rheumatology specialists in TNF-alpha infusion (EP).

Trial protocol and assessments

The protocol was performed with the participants, receiving either a single infliximab infusion (Remicade®, 100 mg, Janssen-Cilag Farmacêutica Ltda.) at a dose of 3 mg/Kg, which was first reconstituted with 10 mL of sterile water for injection and then diluted to 250 mL with sterile 0.9% sodium chloride for injection according to manufacturer's instructions; or receiving a single-infusion placebo, consisting of 250 mL, with sterile 0.9% sodium chloride for injection. Subjects received the intravenous infusions over a two-hour period with a flow rate of 125 mL/h. No other drug was co-administered. Crossover to the following arm of treatment (placebo or infliximab infusion) was made after a washout period of 40 days.

Trial assessments of the study consisted of three steps (assessments in the baseline, immediately after infusion, and seven days after infusion). At the baseline visit (before infusions - T0), anthropometric, office, central (pulse wave analysis-PWA) BP, and ABPM levels and flow-mediated dilation (FMD) were assessed. Moreover, blood samples were collected to further determine inflammatory biomarkers. Continuous beat-to-beat noninvasive hemodynamic recording were evaluated for 15 minutes in the baseline (T0) and immediately after (T1) both infusions. Office BP and blood collection were also examined immediately after both infusions (T1). To assess a short-term response due to the long half-life of infliximab (around 8 days),⁸ seven days after the infusions (T2), office, central, ABPM BP, FMD, and blood collection were reevaluated (Supplementary Figure).

After the trial assessments, a 40-day period of washout was conducted. The treatment was then changed (meaning that the participant who had received saline infusion, after a 40-day period of washout, received infliximab infusion, and vice-versa; the participant who had received infliximab infusion, after a 40-day period of washout, received saline infusion), and the trial assessments were repeated (Supplementary Figure).

No participant changed their antihypertensive medication during the period of the trial. All procedures were begun at 08:00 a.m., and the parameters were evaluated after 8 hours of overnight fasting. After the protocol, patients still remained under observation for 1h before being discharged. Participants were instructed to report either common side effects of infliximab or any adverse event they could have at any time during the study.

Blood pressure, endothelial function, and biochemical assessments

Office SBP and diastolic BP (DBP) were assessed in three steps of the study – in the baseline, immediately after infusion, and seven days after infusion (infliximab and placebo) – by a trained health professional, following the European and Brazilian guidelines of arterial hypertension. A validated digital sphygmomanometer (HEM-907XL, OMRON Healthcare Inc., Bannockburn, IL, USA) was used. Ambulatory BP measurement was assessed in two steps of the study – in the baseline and seven days after infusion (infliximab and placebo) – and performed using an automatic oscillometric monitor (Spacelabs90207, Spacelabs Inc, Redmon, WA). Patients were instructed to maintain normal daily activities and record their 24-hour activities in a personal diary.

Central systolic and diastolic aortic BP and pulse pressure were assessed in two steps of the study – in the baseline and seven

days after infusion (infliximab and placebo) – and determined by PWA, using the Sphygmocor system (Artcor, Sidney, Australia).⁹ The pulse wave was obtained by the method of applanation tonometry of the radial artery. The equipment also provides additional data regarding the measurement of arterial stiffness by the augmentation index (AIx) as well as by AIx corrected for heart rate of 75 bpm (AIx@75). AIx is defined by the ratio between the reflected and the ejection waves (pulse wave traveling from carotid to femoral arteries).

Continuous beat-to-beat non-invasive hemodynamic data were assessed in two steps of the study – in the baseline and immediately after infusion (infliximab and placebo) – and were obtained using the Finometer® device (Finapres Medical Systems; Amsterdam, Netherlands) and Finometer® Beatscope Easy software, version 02.10 (Finapres Medical Systems, Amsterdam, Netherlands). An appropriately sized cuff was placed on the third or fourth left finger, and the arm was rested on a table with the subject in a sitting position. Systolic (SBP in mmHg), diastolic (DBP in mmHg), and mean (MBP in mmHg) BP levels, cardiac output (CO in l/min), and total peripheral resistance (TPR in dyn.s/cm⁻⁵) were recorded for 15 minutes before and immediately after the protocol of infusions. For analyses, the stable section of beat-to-beat recordings were used (10 minutes at the beginning of recordings were excluded from these analyses). The Finometer® device makes use of the volume-clamp method and provides reliable hemodynamic measures, as previously shown.^{10,11}

The endothelial function was assessed in two steps of the study – in the baseline and seven days after infusion (infliximab and placebo) – and was determined by the FMD method, in accordance with current guidelines.^{12,13} Linear vascular transducer (7–12MHz, Toshiba Powervision 6000, Tokyo, Japan), synchronized with an electrocardiogram (ECG) signal, was used in the protocol. Subjects in a supine position in a quiet, air-conditioned room (22–24°C) were submitted to brachial artery occlusion for five minutes, using an aneroid sphygmomanometer. Brachial artery diameter was recorded before and after cuff compression. Change in the brachial artery diameter was expressed as a percentage change relative to the vessel diameter immediately before cuff inflation. The vascular function examination was performed by only one experienced blinded examiner. The intraobserver coefficient of variation was 1.6%.

Blood samples were collected for assessment in three steps of the study – in the baseline, immediately after infusion, and seven days after infusion (infliximab and placebo) – of the plasma levels of nitrate/nitrite; inflammatory biomarkers, such as TNF- α , interleukins-6 (IL-6), and -10 (IL-10); adiponectin; monocyte chemoattractant protein-1 (MCP-1); and the cortisol and aldosterone hormones. For nitrate and nitrite measurements, heparinized plasma was collected and immediately mixed with a nitrite-preserving solution in a 5:1 dilution, containing 0.8M ferricyanide and 1% NP-40.¹⁴ The samples were deproteinized with methanol (1:1) and centrifuged at 14,000g for 5 min. After, 300 μ l of supernatant were injected into the acidified triiodide solution and purged with nitrogen line with a gas-phase chemiluminescent nitric oxide (NO) analyzer (Sievers Model 280i NO Analyzer, Boulder, CO, USA). Inflammatory biomarkers and hormones were measured in EDTA-collected plasma samples and analyzed by enzyme-linked immunosorbent assay (R&D Systems, Minneapolis, MN, USA), according to manufacturer's instructions.

Primary and secondary endpoints

Our primary endpoint was the acute change (from T0 to T1) in mean BP levels relative to the baseline immediately after the infusion, obtained by continuous beat-to-beat non-invasive hemodynamic assessment.

Secondary endpoints included changes in: (1) BP levels determined by office in all timelines, ambulatory, and central measurements after seven days; (2) endothelial function after 7 days; and (3) inflammatory biomarkers in all timelines, after infliximab infusion compared with placebo. All secondary outcomes were exploratory but were considered relevant in this population due to the nature of the trial – pilot proof-of-concept.

Statistical analyses

This study estimated a minimum sample size of 10 RH individuals, to detect a clinical difference in mean BP of 10 mmHg (standard deviation of 10 mmHg) – between infliximab and placebo – power of 80% and alpha error of 0.05.

Continuous variables were expressed as mean and standard deviation (SD), since their normal distribution was assessed by the Kolmogorov–Smirnov test. Categorical variables were presented in frequencies and percentages. Paired Student's t-test was applied to compare delta values (normal distribution) between the application of infliximab and placebo in the same patients (crossover design). A two-way repeated measure ANOVA, followed by a Sidack's post-hoc multiple comparison test, was performed to identify differences between the treatments (infliximab versus placebo) in the delta values of the evaluation times (i.e. T1-T0 – acute, and T2-T0 – 7 days).

The analyses were performed using the software SPSS (IBM SPSS Statistics for Mac, Version 21.0. Armonk, NY: IBM Corp. Released 2012) and GraphPad Prism (version 7.00 for Windows, GraphPad Software, La Jolla California USA, www.graphpad.com). The level of significance accepted was $\alpha=0.05$.

Results

From March 2015 to July 2017, a total of 10 subjects with RH were included in this study, and all subjects completed this proof-of-concept interventional trial (Figure 1). Baseline characteristics of the RH subjects are presented in Table 1. Most participants were male and non-white. As expected, they were mainly obese with T2D, and taking diuretics and a great proportion of β -blockers, angiotensin II receptor antagonists, and calcium channel blockers.

The primary endpoint analysis showed an acute decrease in mean BP values from baseline after infliximab infusion, when compared to the placebo (the mean of differences $\pm$ SD was -6.3 ± 7.2 mmHg, $p=0.02$). Absolute delta mean BP values relative to baseline immediately after the placebo and infliximab infusions in the studied subjects are shown in Figure 2, while the other beat-to-beat hemodynamic parameters are shown in Figure 3. Apart from the decrease in mean BP, this study also found a reduction in diastolic BP levels (-4.9 ± 5.5 mmHg, $p=0.02$) from baseline, after infliximab, when compared to the placebo. No statistically significant differences were identified in SBP, CO, and TPR.

Secondary endpoints are shown in Supplementary Tables 1 and 2. No changes in office BP and HR relative to assessed delta times, T1-T0 and T2-T0, after the treatments were found. Similarly,

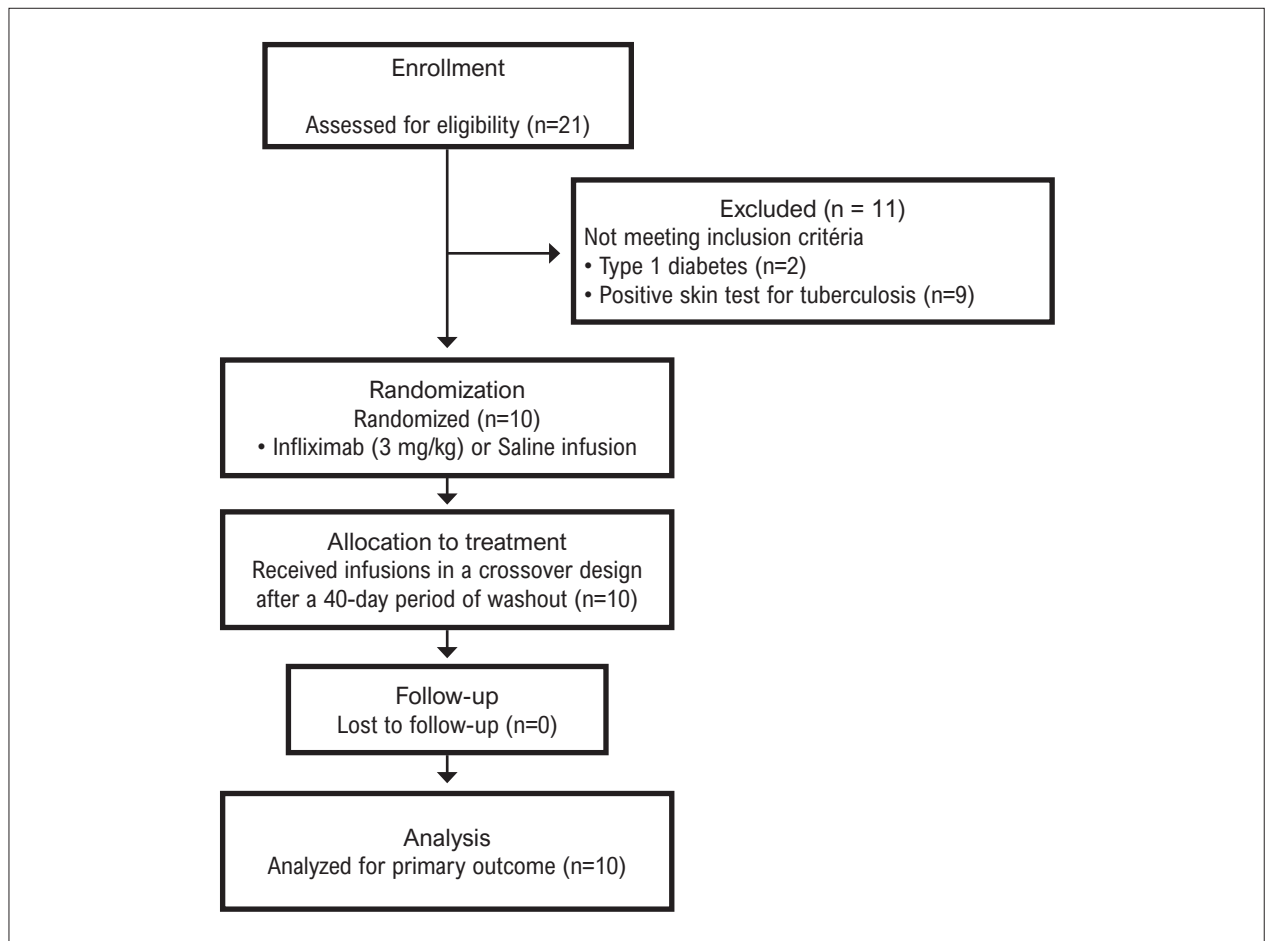


Figure 1 – Study flow diagram.

Table 1 – Baseline characteristics of the studied subjects

	RH (N=10)
Clinical data	
Age (years)	61.8 ± 8.5
Gender (Female)	40% (4)
BMI (Kg/m ²)	31.9 ± 5.9
Type 2 Diabetes, (n)	70% (7)
Non-white, (n)	60% (6)
Anti-HA drugs	
Total number	4.4 ± 0.7
Diuretics, (n)	100% (10)
Spironolactone, (n)	50% (5)
β-blockers, (n)	80% (8)
ACEis, (n)	30% (3)
ARAs II, (n)	70% (7)
CCBs, (n)	90% (9)
Alpha-2 agonists, (n)	12% (1)

Data were expressed as mean and standard deviation, or percentage and absolute number. RH: resistant hypertension; BMI: body mass index; Anti-HA: antihypertensive; ACEis: angiotensin converting enzyme inhibitors; ARAs II: angiotensin II type I receptor antagonists; CCBs: calcium channel blockers.

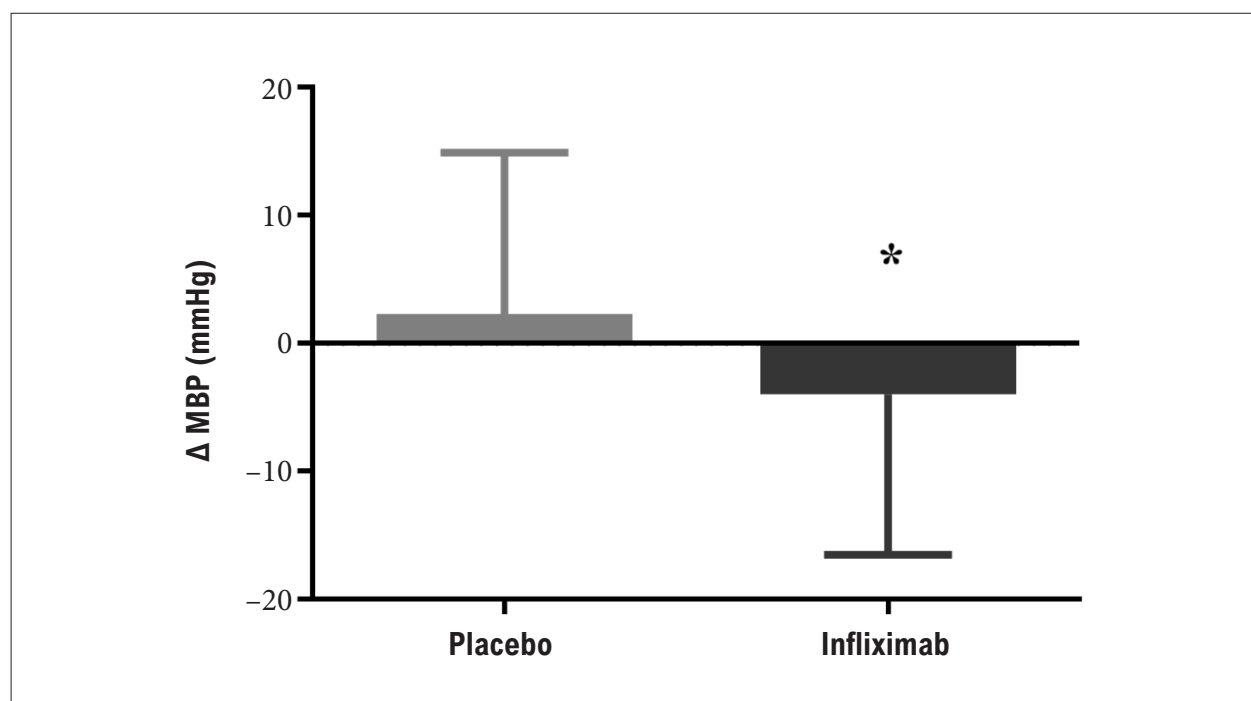


Figure 2 – Absolute delta mean blood pressure (Δ MBP, 2.3 ± 12.6 vs. -4.0 ± 12.5 mmHg, $p=0.02$) relative to baseline immediately after (T1-T0) the placebo and infliximab infusions, respectively, in the studied subjects. Data were expressed as mean and standard deviation. Paired Student's *t*-test was applied to compare delta values between infliximab and placebo. * $p<0.05$ versus placebo.

plasma levels demonstrated no alteration in either inflammatory or hormonal parameters in assessed delta times, except for TNF- α , which increased continuously after a single dose of infliximab, when compared to the placebo (Supplementary Table 1). No difference in delta values of both ambulatory and central BP levels seven days after the infusions (T2-T0). The endothelial function assessed by FMD also remained unchanged (Supplementary Table 2).

Finally, no adverse events were reported by the volunteers during the protocol of the infusions, nor throughout the trial period. There were no overt allergic reactions to infliximab, and no patient withdrew from the study because of toxicity.

Discussion

The main finding of this proof-of-concept pilot trial was that a single dose of infliximab reduced the mean BP levels compared with placebo in subjects with RH. Secondarily, infliximab also reduced diastolic BP. To the best of our knowledge, the present study is the first to investigate effects of the infusion of a monoclonal antibody biologic drug in the RH population.

Several experimental and clinical studies have demonstrated the role of the proinflammatory cytokine TNF- α on hypertension.^{3,15} A crosstalk between TNF- α and renin-angiotensin-aldosterone system (RAAS) has been supported by the literature highlighting their interaction in modulating a hypertensive response and TOD related to it.³ It is well recognized that RH with coexisting comorbidities such as obesity, T2D, and metabolic syndrome,^{16,17} presents overactivation of both the sympathetic nervous system (SNS) and RAAS. Therefore, it is presumed that TNF- α would be

increased in this high-risk population. In fact, our research group has previously shown that TNF- α levels are increased in RH when compared to normotensives and that this cytokine was associated with increased arterial stiffness.² Recently, our research group also demonstrated that an elevated inflammatory score, combining several circulating cytokines, such as the TNF- α , relates to RH in an obesity-dependent manner, when compared to controlled hypertensives.¹

Inhibitors of TNF- α have been acknowledged worldwide to treat autoimmune diseases, mainly in a rheumatology setting.^{18,19} Infliximab is a chimeric human-mouse monoclonal antibody biological drug that neutralizes the biological activity of TNF- α . Binding with high affinity to the soluble and transmembrane forms of TNF- α , infliximab is able to inhibit TNF- α binding with its receptors.²⁰ Besides the clinical benefits observed after infliximab use in relieving symptoms or avoiding the progression of autoimmune diseases, its administration has also revealed the potential to reduce CV risk. For instance, results from cohort studies have indicated a reduction in the incidence of CV events in subjects with rheumatoid arthritis (RA) who were taking anti-TNF- α therapy.^{21,22}

TNF- α inhibition effects on preventing the rise in BP levels and organ damage have been reported in hypertensive models.^{6,23} Our research group found a reduction in SBP and left ventricular hypertrophy in spontaneously hypertensive rats after an 8-week treatment with infliximab (in both doses of 1.5 and 6mg/kg/week). These CV benefits were possibly achieved due to a vasodilation dependent-mechanism, in which the neutralization of TNF- α was able to induce the NO synthesis.⁶ In the clinical setting, infliximab (initially at 3mg/Kg every 8 weeks during a 1-year follow-up)

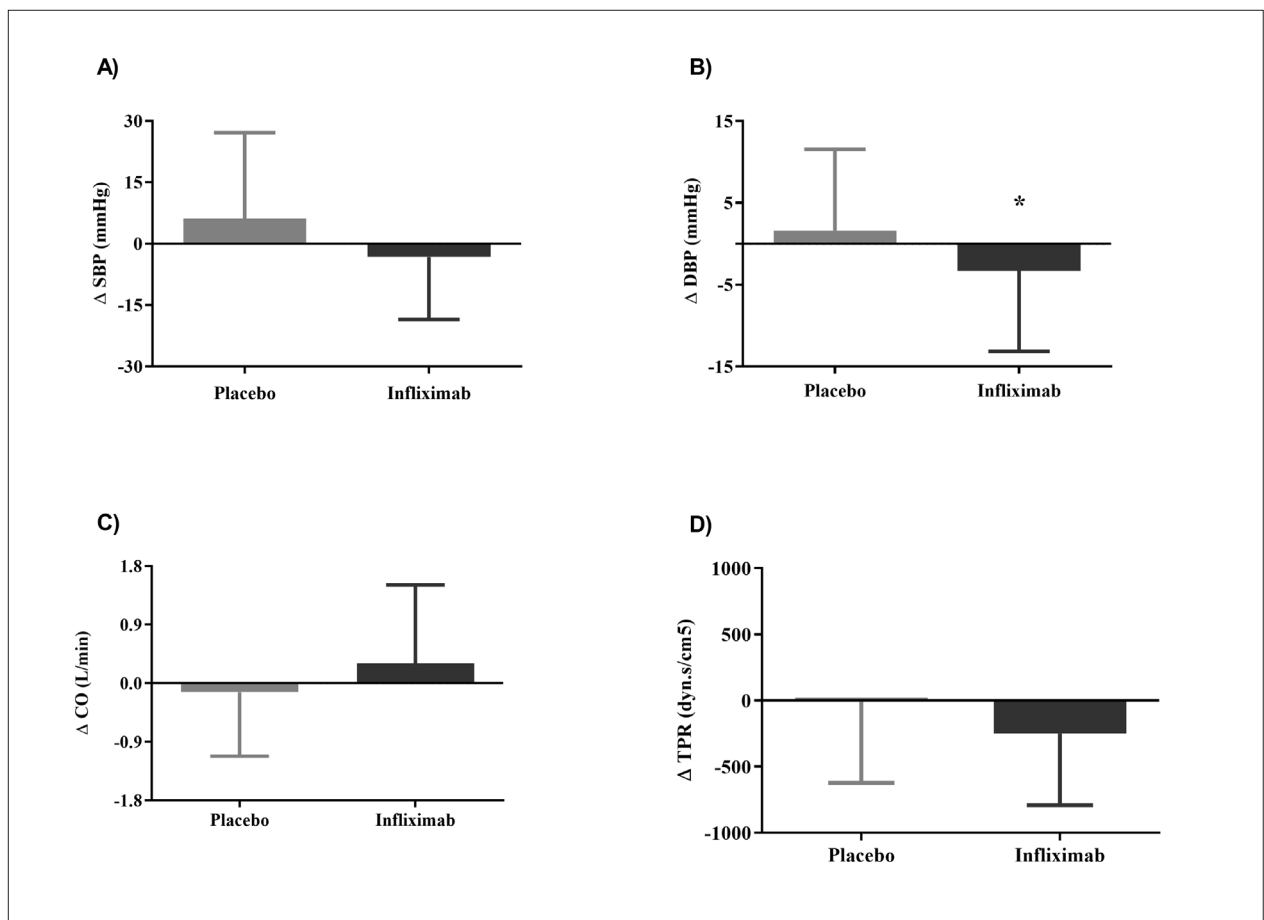


Figure 3 – Absolute deltas of beat-to-beat hemodynamic parameters relative to baseline immediately after (T1-T0) placebo and infliximab infusions, respectively, in the studied subjects. A. Delta systolic blood pressure (Δ SBP, 6.1 ± 21.1 vs. -3.3 ± 15.2 mmHg, $p=0.16$); B. Delta diastolic blood pressure (Δ DBP, 1.6 ± 9.9 vs. -3.3 ± 9.8 mmHg, $p=0.02$); C. Delta cardiac output (Δ CO, -0.14 ± 0.98 vs. 0.30 ± 1.21 mmHg, $p=0.44$); D. Delta total peripheral resistance (Δ TPR, -6.9 ± 615 vs. -248 ± 543 mmHg, $p=0.12$). Data were expressed as mean and standard deviation. Paired Student's t-test was applied to compare delta values between infliximab and placebo. * $p<0.05$ versus placebo.

decreased SBP and DBP levels in patients with recent-onset RA, apart from the reduction in disease activity.²⁴ In addition, after 2 weeks of therapy, infliximab (3mg/kg) reduced 24-h systolic BP in patients with RA, particularly during daytime. This study also found a reduction in plasma levels of norepinephrine and plasma renin activity, suggesting the infliximab-related changes in the SNS and RAAS.²⁵ Our findings are in part consistent with those previous studies, since they revealed a modest effect of a single dose of infliximab therapy at 3 mg/Kg on reducing BP levels immediately after its infusion in a high-risk population such as the RH. Nevertheless, we recognize the failure to reach the targeted clinical difference of 10 mmHg designed in this trial.

Inhibition of the inflammatory pathway by the anti-TNF- α infliximab in our study might have acutely evoked some functional/biochemical changes, and, consequently, provided these reduced BP levels. As is well-known, TNF- α is able to induce endothelial dysfunction²⁶ by (i) stimulating the release of endothelial microparticles and reactive oxygen species production²⁷ and (ii) downregulating the expression of constitutive eNOS,²⁸ which reduces NO bioavailability. In our study, FMD results showed no statistical difference seven days after the acute administration of

infliximab, nor in the levels of NO metabolites (nitrate/nitrite), in either of two assessed times. Although TNF- α inhibition has been reported as a potential strategy to improve endothelial function,²⁹ our negative results might be explained by the fact that we have previously demonstrated that RH subjects have severely impaired vasodilation associated with greater vascular stiffness³⁰ and higher levels of 8-isoprostane,³¹ a proposed marker of oxidative stress *in vivo*, when compared to controlled hypertensives. On the other hand, it is still possible that NO levels immediately after infliximab infusion are reduced in small resistance arteries – which our study was unable to access – causing the TPR and BP reductions, although the first parameter proved to be insignificant. Another hypothesis to support our findings is the crosstalk between TNF- α and RAAS, as already mentioned above. This proinflammatory cytokine can stimulate both the expression of the angiotensin type 1 receptors¹⁵ and the angiotensinogen gene in the liver,³² the latter physiologically leading to high levels of angiotensin II and subsequent secretion of aldosterone. Only the aldosterone levels were assessed in our study. Although the aldosterone result was borderline, and this hormone may act in a long-term regulation of BP, a trend could be observed toward a greater reduction

in aldosterone in both times assessed after infliximab, when compared to placebo.

Interestingly, TNF- α levels gradually increased in the times assessed after infliximab use, when compared to the placebo. Similarly, some studies have found an increase in their levels after anti-TNF- α therapy,^{29,33} although the mechanisms for this elevation are still unknown. This may well be explained by the prolongation of the TNF- α half-life by treatment – as previously observed in studies exploring other anti-TNF- α therapy^{34,35} – despite having blocked the TNF- α activity.³⁴ On the other hand, a chronic treatment was associated with the decrease in TNF- α levels, achieving a lower steady state level, which may reflect an equilibrium between tissue production and the elimination of TNF- α .³⁶ Interestingly enough an acute decrease in BP levels was observed, which was not maintained after seven days of follow-up. Since it is known that the TNF- α levels increased in the week following infliximab infusion, and that chronic treatment tends to decrease its levels, it is reasonable to suppose that a chronic treatment could be accompanied by a sustained decrease in BP levels. However, this would need to be proven in a longer follow-up after infusion.

The present study has several limitations inherent to pilot, proof-of-concept studies. The most important limitation is the small sample size. It is worth mentioning that our studied population represents a very specific subset of hypertensive patients, with a low prevalence worldwide.¹⁶ Moreover, a great proportion of the subjects presented positive skin tests for tuberculosis and were excluded from the study (n=9). Our negative findings in secondary outcomes in the two assessed times may have been due to an insufficient statistical power (type II error). A single dose at 3mg/Kg may not have been enough to cause the clinical effect expected immediately after the infusion, nor any effect in the short-term evaluation (seven days after infusion). Although we did not find the targeted difference of 10 mmHg in mean BP after infliximab versus placebo [in fact, the mean of differences was -6.3 (SD=7.2)], our study power was 70% and may therefore be considered satisfactory, since it is a pilot trial. We recognize that a crossover design may imply the possible existence of carry-over effects. Trying to overcome this issue, and given the long half-life of infliximab (median elimination half-life is about eight days),⁸ a washout of 40 days (5x half-life) would be safe. Due to the single dose used in this trial, it is not possible to assure that the effects in reducing BP levels are sustained during the chronic use of infliximab. Finally, to guarantee internal and external validities

larger-scale trials would be required to establish the clinical safety and efficacy of a TNF- α inhibitor in the management of RH.

Conclusions

This proof-of concept pilot trial showed that a single-dose infliximab reduced the mean and diastolic BP levels immediately after its infusion, when compared to the placebo. The anti-TNF- α therapy was found to be safe and well-tolerated. It adds clinical perspective on therapies targeting the inflammatory process to manage difficult-to-treat hypertension. Due to the small sample size and power below the pre-specified levels, the findings must be interpreted as exploratory and hypothesis-generating.

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Author contributions

Conception and design of the research: Faria AP, Modolo R, Moreno H; Acquisition of data and Critical revision of the manuscript for intellectual content: Faria AP, Ritter AMV, Santa-Catharina A, Souza DP, Naseri EP, Bertolo MB, Pioli MR, Carvalho CC, Modolo R, Moreno H; Analysis and interpretation of the data: Faria AP, Ritter AMV, Santa-Catharina A, Modolo R; Statistical analysis and Writing of the manuscript: Faria AP; Obtaining financing: Faria AP, Bertolo MB, Moreno H.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

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*Supplemental Materials

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New Perspectives in the Treatment of Hypertension

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Short Editorial related to the article: Effects of Anti-TNF- α Therapy on Blood Pressure in Resistant Hypertensive Subjects: A Randomized, Double-Blind, Placebo-Controlled Pilot Study

Arterial hypertension is by far the biggest risk factor for cardiovascular diseases. Thiocyanates, barbiturates, bromides and bismuth were tested in the treatment of arterial hypertension in the early 1940s.¹ The use of these drugs was discontinued because they were proven ineffective and had several side effects. In the mid-1950s, ganglion blockers such as hexamethonium, pentolinium, mecamlamine and peripherally acting sympatholytic substances (guanethidine) were tested as treatment of arterial hypertension and were shown effective in reducing blood pressure, but little tolerated.² New drugs were introduced to treat hypertension in the 1950s, including diuretics.³

In 1956, in an observational study, Moser and Magaulay followed up 106 hypertensive patients who received rauwolfia, hydralazine, reserpine, mecamlamine and chlorothiazide as treatment for arterial hypertension, alone or in combination. The dose of chlorothiazide used in this study ranged from 0.5 to 1.5 grams and the combination of chlorothiazide resulted in better control of blood pressure. Since that observational study by Moser and Magaulay to the present day, several studies related to the pharmacological treatment of hypertension have been carried out.⁴ The first randomized, placebo-controlled study conducted on the treatment of arterial hypertension was the Veterans Administration (VA), published in 1967.⁵ It is worth noting that the study inclusion criterion for active versus placebo treatment was diastolic pressure between 115 and 129 mmHg. After the publication of the VA-I study in 1967⁵ and the VA-II in 1970,⁶ several randomized controlled studies addressing the treatment of arterial hypertension were carried out. The initial focus of treatment for arterial hypertension was renal sodium excretion, as renal disorders were initially thought to be the main cause of hypertension. Subsequently, the pathophysiological mechanisms of hypertension were elucidated and the therapy was directed to the main pathophysiological mechanisms. The activation of the sympathetic nervous system as an important pathophysiological mechanism of hypertension had already been perceived in the 1950s,

and various forms of sympathetic nervous system block and even sympathectomy were then attempted.⁷ Beginning in the 1980s, with the introduction of the microneurography and the norepinephrine spillover technique, the importance of activation of the sympathetic nervous system in the pathophysiology of hypertension was even more evident.^{8,9} Although poorly tolerated, central and peripheral adrenergic blockers have always been part of the treatment of arterial hypertension.¹⁰ The activation of the renin-angiotensin aldosterone system (RAS) and the altered natriuresis pressure curve are two other important mechanisms in the pathophysiology of arterial hypertension. Currently, the use of diuretics to correct the altered natriuresis pressure curve and inhibitors of the renin-angiotensin aldosterone system, which act at different sites, has been routine in the treatment of arterial hypertension.¹¹

The sympathetic nervous system and the renin-angiotensin aldosterone system are involved directly in the pathophysiological mechanisms of arterial hypertension. An important aspect in this sense is that the activation of these two systems is related to an inflammatory process in the hypertensive patient.¹² They interact with inflammatory cytokines such as interleukin-6 (IL-6) and the tumor necrosis factor- α (TNF- α). The sympathetic nervous system stimulates the secretion of proinflammatory cytokines and at the same time it functions as a source of cytokines.¹³ Angiotensin-II is an important proinflammatory factor. It is related to the production of TNF- α and IL-6 and stimulates the monocyte chemoattractant protein-1 (MCP-1) and the nuclear factor-B.^{14,15} On the other hand, the type of drug used in the treatment of hypertensive patients can reduce the inflammatory process related to hypertension. The use of centrally acting sympatholytic moxonidine in the treatment of postmenopausal hypertensive women resulted in a reduction in TNF- α .¹⁶

In a study involving patients with resistant hypertension, Barbaro et al.¹⁷ found higher TNF- α values in patients with resistant hypertension compared to the normotensive group.¹⁷ The results point to TNF- α as a possible mediator of vascular damage in patients with resistant hypertension. Bautista et al.¹⁸ found an association of IL-6 and TNF- α levels with blood pressure values, regardless of age, sex, body mass index, family history of hypertension and other proinflammatory cytokines. In the study,¹⁹ the authors evaluated Infliximab, a drug that inhibits TNF- α , for the treatment of resistant hypertensive patients. Infliximab in a single dose of 3 mg/kg (infusion) resulted in a drop of 6.3 mmHg in mean arterial pressure and 4.9 mmHg in diastolic pressure. This acute effect of Infliximab on blood pressure opens a new perspective in the treatment of arterial hypertension. Regardless of the drop in blood

Keywords

Hypertension/trends; Blood Pressure; Diuretics/therapeutic use; Cardiovascular Diseases/complications; Drug Therapy/trends.

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pressure, using anti-TNF- α blocks a factor that can be aggravating in vascular injuries. It is known that the severity of hypertension is related to a vicious circle resulting from the activation of pressure systems (sympathetic nervous

system and renin-angiotensin aldosterone system).²⁰ The interruption of this circle is essential to protect the organism and for a better action of hypotensive drugs already well known.

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Validation of a Simple Electrocardiographic Algorithm for Detection of Ventricular Tachycardia

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Abstract

Background: The differential diagnosis of wide QRS complex tachycardia (WCT) between ventricular tachycardia (VT) or supraventricular tachycardia with aberrant conduction (SVT-A) is sometimes difficult in the emergency room.

Objective: The aim of this study was to evaluate the accuracy of a new simple electrocardiographic algorithm to recognize VT in patients with wide complex tachycardia.

Methods: The 12-lead electrocardiograms (ECG) for WCT were prospectively obtained from 120 patients during electrophysiological study. Six physicians with different expertise analyzed the electrocardiographic recordings, and made the diagnosis based on the D12V16 algorithm, that involves the analysis of the predominant polarity of QRS in leads I, II, V1 and V6. The diagnosis was compared with that made using the traditional Brugada algorithm and the “gold-standard” electrophysiological study. Statistical analyses were performed with a significance level of 5% ($p < 0.05$).

Results: According to the EPS study, 82 ECG recordings were VT and 38 SVT-A. Structural heart diseases were present in 71 (86.6%) patients with VT and in 8 (21.1%) with SVT-A. The Brugada algorithm had higher global sensitivity (87.2%), and the D12V16 algorithm had higher global specificity (85.1%) for VT. Both D12V16 and Brugada’s algorithms presented a high positive predictive value (90.9% vs 85.8%, respectively) and similar accuracy (73.8% vs 81.4%, respectively) for the diagnosis of VT. Experienced evaluators were more accurate using Brugada algorithm than the D12V16 algorithm, but the accuracy of both algorithms was similar according to less experienced examiners.

Conclusion: The simplified algorithm may be a useful method to recognize VT in the ECG, especially for less experienced doctors. (Arq Bras Cardiol. 2021; 116(3):454-463)

Keywords: Tachycardia Supraventricular; Tachycardia Ventricular; Arrhythmias Cardiac; Electrocardiography.

Introduction

The recognition of ventricular tachycardia (VT) as the mechanism of wide complex tachycardia (WCT) is an important issue, since an incorrect electrocardiographic (ECG) analysis may lead to inappropriate therapy. In addition, the VT diagnosis also allows more appropriate acute and long-term management of the patient and prevents hospitalizations and unnecessary exams.^{1,2}

Since the 1960s, many ECG criteria have been proposed in an attempt to differentiate VT from supraventricular tachycardia with aberrant conduction (SVT-A).³⁻¹⁰ Many of them consider that specific measurements in milliseconds result in difficult memorization, low reproducibility of accuracy, and poor clinical applicability. Additionally, in emergency medicine, there is a high rate of discordance between observers, with a low diagnostic accuracy,¹¹⁻¹³ that could lead to a harmful treatment.¹⁴

Therefore, the development of a simple method, preferably visual and easily memorized by resident physicians in the emergency department, regardless of expertise in arrhythmia, could improve clinical decisions.

The discriminative power of ECG leads I, II, V1 and V6 to identify the mechanisms of WCT was initially proposed by Nagi et al.,¹⁵ but it has not been prospectively validated. The aim of this study was to evaluate the diagnostic accuracy of a simplified, easily memorized method for the differential diagnosis of WCT.

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Material and Methods

The research protocol was approved by the Scientific Committee of the Heart Institute, Instituto do Coração - HC-FMUSP, as well as by the Research Ethics Committee of the Messejana - Dr. Carlos Alberto Studart Gomes (HM) - Hospital, under protocol number 336.107.

Patients and Electrocardiogram

We selected ECG recordings from 120 consecutive patients (one per patient) presented with WCT in the electrophysiological study (EPS) performed in our center between January 2007 and December 2013.

After receiving information about the study, patients willing to participate signed an informed consent form. The study was conducted according to the ethical principles in research involving humans.

WCT was defined by EPS, as a heart rate ≥ 100 bpm in the absence of visible conducted sinus P wave and a QRS duration ≥ 120 ms. These ECG tracings were recorded in the EPS and obtained prospectively and consecutively. Patients with WCTs who were taking antiarrhythmic medications, patients with pre-excited tachycardia, and those patients with artificial cardiac pacemakers were excluded. After selecting the 12-lead ECG, we collected the following clinical variables from each patient: age, gender, and presence or absence of structural heart disease.

The D12V16 algorithm based on the analysis of leads I, II, V1 and V6

All ECG recordings were analyzed according to the simplified algorithm using three steps (Figure 1): (1) In the first step, VT was considered if the four leads (I, II, V1, and V6) had a predominantly negative polarity (R/S ratio < 1). In the absence of these findings, we proceeded to the next step. (2) In the second step, VT was diagnosed if at least three of the four leads displayed a predominantly negative polarity. If this step was not fully completed, we proceeded to the next step. (3) In the third step, VT was diagnosed if at least two of the four leads displayed a predominantly negative polarity (I or V6 necessarily included). If all these steps were not fully completed, the diagnosis assumed was SVT-A. Figures 2, 3 and 4 present all the steps of the algorithm.

ECG Examiners and ECG Analysis

The ECGs were analyzed by three pairs of examiners: (1) two cardiologists with expertise in clinical arrhythmia; (2) two general cardiologists; and (3) two resident physicians of the emergency department. The use of magnifying glasses was allowed if necessary.

The electrocardiograms were analyzed by the six examiners in four different moments: (A) using the Brugada algorithm;⁶ (B) using the D12V16 algorithm; (C) repeating the analysis using the Brugada algorithm with clinical information; and (D) repeating the analysis using the D12V16 algorithm with clinical information.

All ECGs recordings were scrambled, and all examiners were blinded to the EPS diagnosis. Clinical information of

each electrocardiogram was revealed for the examiners after completing moments A and B.

Statistical Analysis

The patients' characteristics are described according to the EPS diagnosis using absolute and relative frequencies. The association between each characteristic and diagnosis was confirmed using chi-square tests. Age of patients was described by mean values and standard deviation and compared according to the diagnosis using unpaired Student's t-test.

The diagnoses were described according to the four steps of ECG analysis, and the results obtained were compared with the EPS. We calculated diagnostic parameters, e.g. sensitivity (Sn), specificity (Sp), positive predictive value (PPV), negative predictive value (NPV) and accuracy. The agreement of each step/method with the EPS was evaluated by the kappa coefficient. We calculated the corresponding 95% confidence intervals for all of the estimated measures.

The analyses were repeated only for the final diagnoses and the groups were separated according to the examiner's experience. For statistical analysis of Sn and Sp we used the total amount ($n=120$) of electrocardiograms interpreted by all the six examiners. Agreements and disagreements with the EPS, considered the gold standard method, were established for each procedure, while the marginal association between the methods was assessed using McNemar's test. Agreements and disagreements between evaluators were also determined in both methods and these procedures were compared using McNemar's test. We compared both methods between the groups of evaluators (variability of the traditional method between different evaluators). The Kolmogorov-Smirnov test confirmed the normality of age distribution. The significance level was established at 5% ($p < 0.05$). The software employed in the statistical analysis was the IBM-SPSS for Windows version 20.0.

Results

Patient characteristics

Patient characteristics are presented in Table 1. According to the EPS, 82 patients presented with VT (68%) and 38 had SVT-A; 81 were men, 69.5% of them had VT and 63.2% had SVT-A. Mean age of the patients was 49.1 ± 17.5 years old. Patients with VT were older than SVT-A patients (52.7 ± 16.3 vs. 41.4 ± 17.8 years old; $p = 0.001$). Structural heart disease was detected in 79/120 (65.8%) patients; 71/82 (86.6%) patients with VT, and in 8/38 (21.1%) patients with SVT-A. Patient characteristics are presented in Table 1.

Global analysis of the algorithms

Values of Sn, Sp, PPV, NPV and accuracy, according to each algorithm step, are presented in Table 2. Six examiners performed a total of 2,880 analyses (720 using the simplified algorithm and the Brugada algorithm, regardless of clinical information). The Sn of the Brugada algorithm was higher than that of the simplified algorithm (87.2% and 68.7%, respectively), while the Sp of the D12V16 algorithm was higher

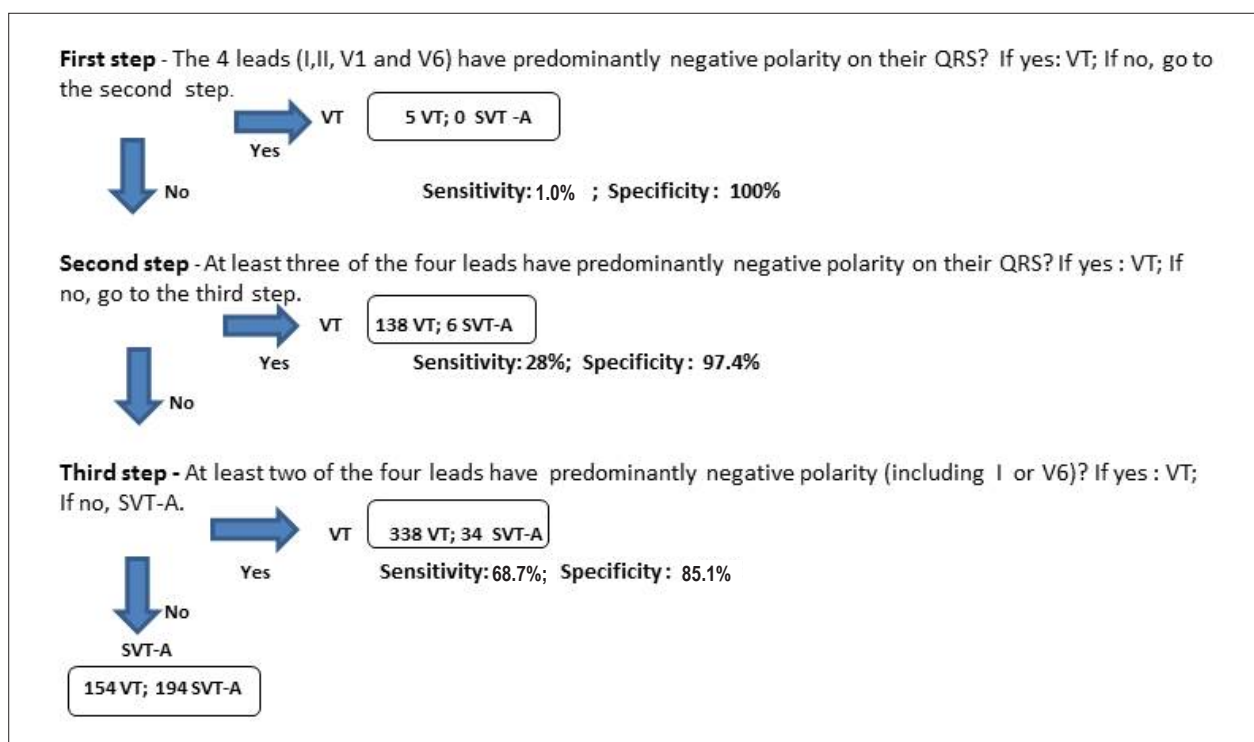


Figure 1 – The simplified I, II, V1 and V6 algorithm. Analysis of 120 electrocardiograms for wide QRS tachycardia performed by six observers (total of 720 analyses); each observer analyzed 82 ventricular tachycardia (VT) and 38 supraventricular tachycardia with aberrant conduction (SVT-A); sensitivity, specificity and the number of ECGs that fulfilled the diagnosis are described in the figure.

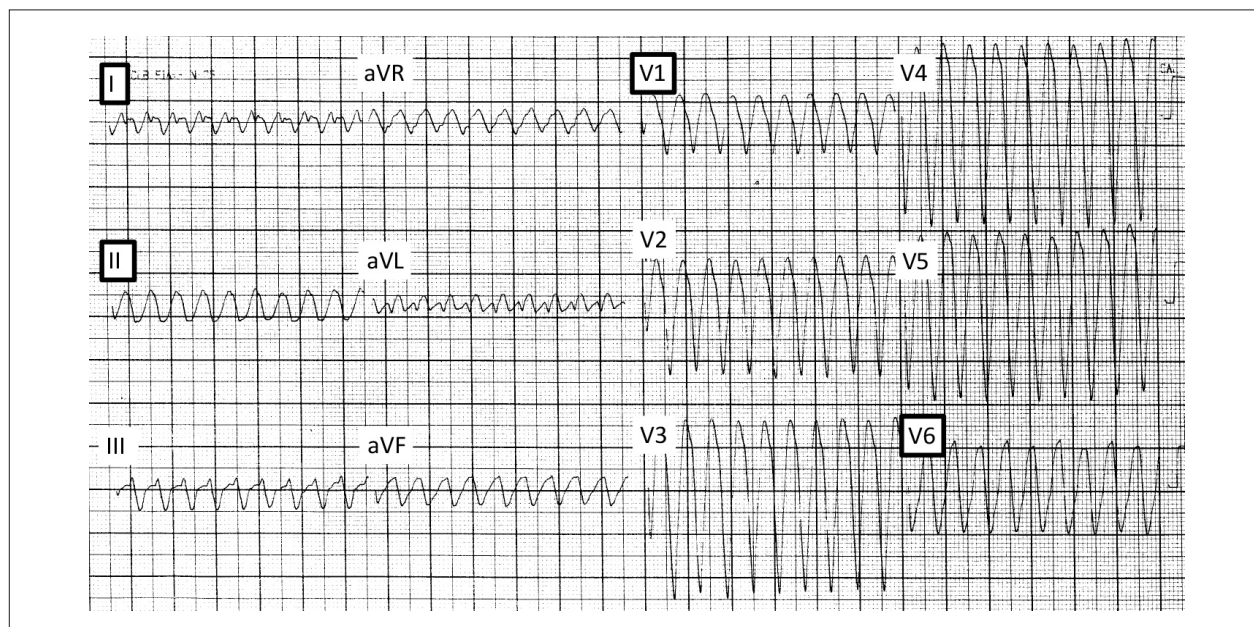


Figure 2 – Example of all four leads with predominantly negative polarity (step 1); these findings have 100% specificity for diagnosis of ventricular tachycardia.

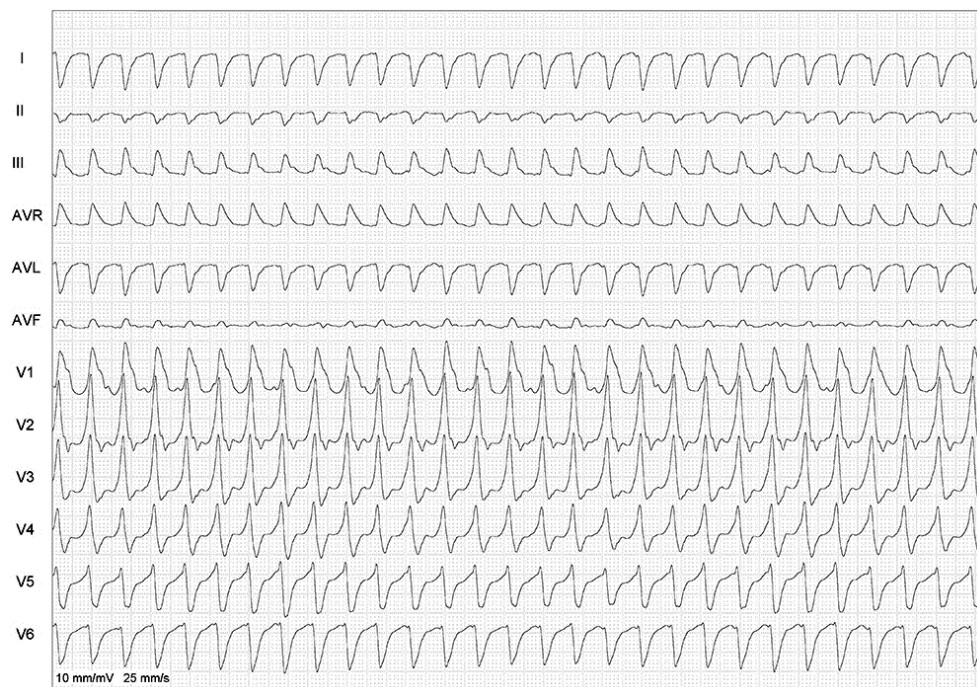


Figure 3 – Wide complex tachycardia, using the simplified algorithm; the predominantly negative polarity of three of the four leads suggests ventricular tachycardia.

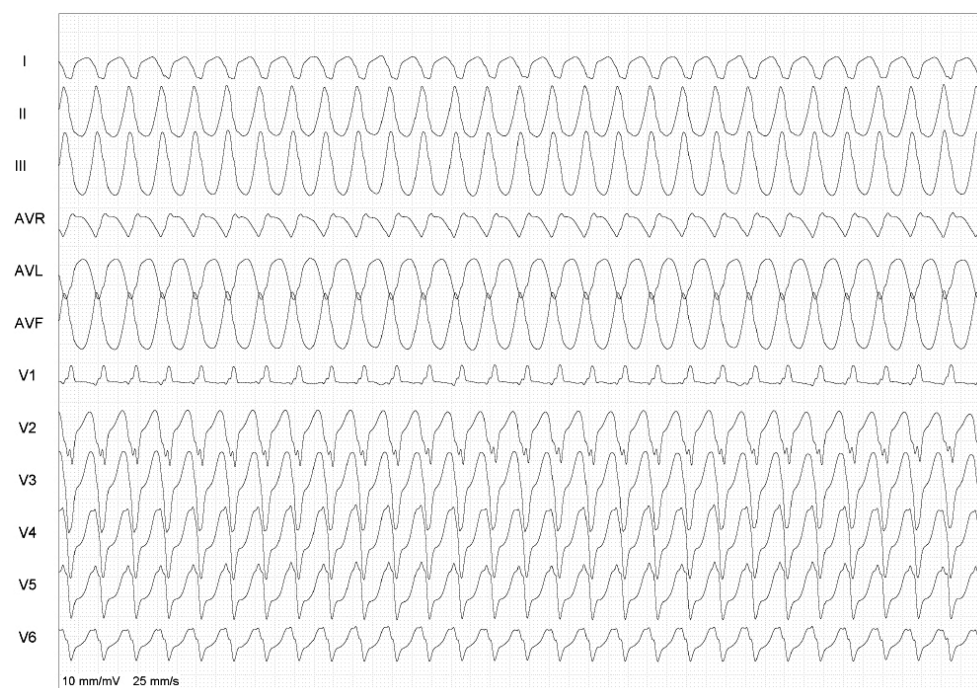


Figure 4 – Example of two predominantly negative polarities (step 3) in four leads (DI, DII, V1 and V6), with inclusion of DI and/or V6 (in this case, both negative).

Table 1 – Clinical characteristics of patients diagnosed with supraventricular tachycardia with aberrant (SVT-A) conduction and ventricular tachycardia (VT) according to the electrophysiological study

Variable	SVT-A (n=38)	VT (n=82)	Total (n=120)	P
Male, n (%)	24 (63.2)	57 (69.5)	81 (67.5)	0.489
Heart disease, n (%)	8 (21.1)	71 (86.6)	79 (65.8)	<0.001
Age, years	41.4±17.8	52.7±16.3	49.1±17.5	0.001*
Chi-square test; *Student's t-test				

Table 2 – Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of each step of the Brugada algorithm and the D12V16 algorithm with and without clinical characteristics

Criterion	Step	Sensitivity for VT Diagnosis, % (95% CI)	Specificity for VT Diagnosis, % (95% CI)	PPV for VT Diagnosis, % (95% CI)	NPV for VT Diagnosis, % (95% CI)	Accuracy, % (95% CI)
Brugada	Step 1	19.7 (16.3-23.5)	91.7 (87.3-94.9)	83.6 (75.6-89.8)	34.6 (30.8-38.5)	42.5 (38.9-46.1)
	Step 2	48.0 (43.5-52.5)	86.8 (81.8-90.9)	88.7 (84.3-92.3)	43.6 (39.0-48.3)	60.3 (56.7-63.9)
	Step 3	61.8 (57.3-66.1)	83.8 (78.3-88.3)	89.1 (85.4-92.2)	50.4 (45.2-55.5)	68.7 (65.3-72.1)
	Step 4	87.2 (83.9-90.0)	68.9 (62.4-74.8)	85.8 (82.4-88.7)	71.4 (64.9-77.2)	81.4 (78.6-84.2)
D12V16 Algorithm	Step 1	1.0 (0.3-2.4)	100 (98.4-99.0)	100 (47.8-100.0)	31.9 (28.5-42.7)	32.4 (29.0-35.8)
	Step 2	28.0 (24.1-32.2)	97.4 (94.4-99.0)	95.8 (91.2-98.5)	38.5 (34.5-42.7)	50.0 (46.3-53.7)
	Step 3	68.7 (64.4-72.8)	85.1 (79.8-89.4)	90.9 (87.5-93.6)	55.7 (50.4-61.0)	73.8 (70.6-77.0)
Brugada with Clinical Data	Step 1	28.0 (24.1-32.2)	89 (84.2-92.8)	84.7 (78.2-89.8)	36.4 (32.4-40.6)	47.4 (43.8-51.0)
	Step 2	49.4 (44.9-53.9)	87.3 (82.2-91.3)	89.3 (85.0-92.7)	44.4 (39.8-49.2)	61.4 (57.8-65.0)
	Step 3	62.0 (57.5-66.3)	83.8 (78.3-88.3)	89.2 (85.4-92.3)	50.5 (45.4-55.7)	68.9 (65.5-72.3)
	Step 4	87.2 (83.9-90.0)	73.7 (67.5-79.3)	87.7 (84.5-90.5)	72.7 (66.5-78.4)	82.9 (80.1-85.7)
D12V16 Algorithm with Clinical Data	Step 1	1.4 (0.6-2.9)	100 (98.4-100.0)	100 (59.0-100.0)	32.0 (28.6-35.5)	32.7 (29.3-36.1)
	Step 2	27.4 (23.5-31.6)	98.7 (96.2-99.7)	97.8 (93.8-99.5)	38.7 (34.7-42.8)	50.0 (46.3-53.7)
	Step 3	65.0 (60.6-69.3)	90.8 (86.3-94.2)	93.8 (90.7-96.1)	54.6 (49.5-59.7)	73.1 (69.9-76.3)

values expressed in % (95% confidence interval, 95%CI); VT: ventricular tachycardia.

than the Brugada algorithm (85.1% and 68.9%, respectively). The PPV for VT was high for both methods (90.9% in the D12V16 algorithm, and 85.8% in the Brugada algorithm). The diagnostic accuracy was 73.8% using the D12V16 algorithm ($k = 0.471$; 95% confidence interval [CI], 0.41–0.53), and 81.4% using the Brugada algorithm ($k = 0.566$; 95% CI, 0.5–0.63). Although not significant, an increase in Sp was observed in the presence of clinical information (90.8% for the simplified algorithm, 73.7% for the Brugada algorithm). A slight increase in accuracy was detected when the Brugada algorithm was applied in the presence of clinical information ($k = 0.607$; 95%CI, 0.54–0.67). No increase in accuracy was observed using the D12V16 algorithm in the presence or absence of clinical information ($k = 0.471$; 95% CI, 0.41–0.53; and $k = 0.474$; 95% CI, 0.42–0.53, respectively).

Analysis results by groups of observers

Values of Sn, Sp, PPV, NPV and accuracy by each group of observers are presented in Table 3. In all three groups, a higher Sn was observed with the Brugada algorithm compared

with the D12V16 algorithm, with no difference between the groups. However, Sp was far more evident in the emergency resident physicians (group III) than in the other groups. Higher diagnostic accuracy was observed when cardiology specialized evaluators (groups I and II) used the Brugada algorithm compared to the simplified D12V16 algorithm (84.6% and 85.8% vs. 74.2% and 74.6%, respectively). For emergency medicine resident physicians (group III), the diagnostic accuracy of the two methods was similar (73.7% using the Brugada algorithm, 72.9% using the simplified algorithm). For these evaluators, the D12V16 algorithm showed a higher Sp than the Brugada algorithm (85.5% and 65.8%, respectively). These values were not significantly different in the presence of clinical information (Table 4).

Diagnosis agreement between evaluators and methods

Data on diagnostic agreement between the six observers based on the analysis of 120 ECGs are presented in Table 5. The percentage of disagreement using the Brugada algorithm and the D12V16 algorithm was 60.8% and 30%, respectively.

Table 3 – Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of each group of observers

Criterion	Group	Sensitivity for VT Diagnosis, % (95% CI)	Specificity for VT Diagnosis, % (95% CI)	PPV for VT Diagnosis, % (95% CI)	NPV for VT Diagnosis, % (95% CI)	Accuracy, % (95% CI)
Brugada	I – Expertise in Arrhythmias	88.4 (82.5-92.9)	76.3 (65.2-85.3)	89.0 (83.1-93.3)	75.3 (64.2-84.4)	84.6 (82.0-87.2)
	II – General Cardiologists	95.7 (91.4-98.3)	64.5 (52.7-75.1)	85.3 (79.4-90.1)	87.5 (75.9-94.8)	85.8 (83.3-88.3)
	III – Emergency Resident Physicians	77.4 (70.3-83.6)	65.8 (54.0-76.3)	83.0 (76.1-88.6)	57.5 (46.4-68.0)	73.7 (70.5-76.9)
D12V16 Algorithm	I – Expertise in Arrhythmias	68.9 (61.2-75.9)	85.5 (75.6-92.5)	91.1 (84.7-95.5)	56.0 (46.5-65.2)	74.2 (71.0-77.4)
	II – General Cardiologists	70.1 (62.5-77.0)	84.2 (74.0-91.6)	90.6 (84.1-95.0)	56.6 (47.0-65.9)	74.6 (71.4-77.8)
	III – Emergency Resident Physicians	67.1 (59.3-74.2)	85.5 (75.6-92.5)	90.9 (84.3-95.4)	54.6 (45.2-63.8)	72.9 (69.7-76.1)
Brugada with Clinical Data	I – Expertise in Arrhythmias	86 (79.7-90.9)	81.6 (71.0-89.5)	91.0 (85.3-95.0)	72.9 (62.2-82.0)	84.6 (82.0-87.2)
	II – General Cardiologists	98.2 (94.7-99.6)	72.4 (60.9-82.0)	88.5 (82.9-92.7)	94.8 (85.6-98.9)	90.0 (87.8-92.2)
	III – Emergency Resident Physicians	77.4 (70.3-83.6)	67.1 (55.4-77.5)	83.6 (76.7-89.1)	58.0 (47.0-68.4)	74.1 (70.9-77.3)
D12V16 Algorithm with Clinical Data	I – Expertise in Arrhythmias	65.2 (57.4-72.5)	94.7 (87.1-98.5)	96.4 (91.0-99.0)	55.8 (46.8-64.5)	74.6 (71.4-77.8)
	II – General Cardiologists	70.1 (62.5-77.0)	88.2 (78.7-94.4)	92.7 (86.7-96.6)	57.8 (48.2-66.9)	75.8 (72.7-78.9)
	III – Emergency Resident Physicians	59.8 (51.8-67.3)	89.5 (80.3-95.3)	92.5 (85.7-96.7)	50.7 (42.0-59.5)	69.1 (65.7-72.5)

Values expressed in % (95% confidence interval, 95%CI).

Table 4 – Agreement and disagreement between the diagnoses made by the Brugada algorithm and the D12V16 algorithm

Evaluation	Brugada	D12V16 Algorithm	p
Without clinical information			
SVT-A agreement, n (%)	157 (21.8)	194 (26.9)	<0.001
VT agreement, n (%)	429 (59.6)	338 (46.9)	
Disagreement, n (%)	134 (18.6)	188 (26.2)	
With clinical information			
SVT-A agreement, n (%)	168 (23.3)	207 (28.7)	<0.001
VT agreement, n (%)	429 (59.6)	320 (44.4)	
Disagreement, n (%)	123 (17.1)	193 (26.9)	

Results obtained using McNemar's test; SVT-A supraventricular tachycardia with aberrant conduction; VT: ventricular tachycardia.

Table 5 – Agreement and disagreement in the diagnoses made by six evaluators who analyzed 120 electrocardiograms using the Brugada algorithm and the D12V16 algorithm

Evaluation	Brugada	D12V16 Algorithm	p
Without clinical information			
SVT-A agreement, n (%)	8 (6.7)	40 (33.3)	<0.001
VT agreement, n (%)	39 (32.5)	44 (36.7)	
Disagreement, n (%)	73 (60.8)	36 (30.0)	
With clinical information			
SVT-A agreement, n (%)	18 (15.0)	43 (35.8)	<0.001
VT agreement, n (%)	40 (33.3)	40 (33.4)	
Disagreement, n (%)	62 (51.7)	37 (30.8)	

Results obtained using McNemar's test; SVT-A supraventricular tachycardia with aberrant conduction; VT: ventricular tachycardia.

In the presence of clinical information, these values were 51.7% and 30.8%, respectively. This difference was statistically significant ($p < 0.001$), both with and without clinical information. Figure 5 shows disagreement between algorithms.

Discussion

Many of the criteria used for the differential diagnosis of a wide QRS tachycardia are based on peculiar aspects of the electrocardiogram, which are quite difficult to memorize, compromising the clinical applicability and consequently leading to a lack of reproducibility.^{7,11} When available, consulting with experts is recommended to reduce diagnostic errors and adverse consequences.² However, one cannot rely on the presence of “experts” in all emergency department facilities.

In 1999, Nagi et al.¹⁵ proposed values of bipolar (I-II) and precordial (V1-V6) leads for the differential diagnosis of WCT, guided by computer software for ECG analysis. The predominance of negative polarity of at least two of the four leads, with lead I or V6 included, made the diagnosis of VT in 89.2% of cases. Although this is an easily applied technique by non-specialists, it has not been evaluated systematically. In our study, we compared the diagnosis obtained by a DI, DII, V1 and V6 polarity analysis (D12V16 algorithm) with the most frequently used algorithm for WCT diagnosis (Brugada Algorithm), in a significant number of patients. We also evaluated the role of clinical information to improve the correct diagnosis rate, which was applied by the physicians, regardless of their arrhythmia expertise. The Sp of the D12V16 method was higher for VT diagnosis and there were lower disagreement coefficients (greater

reproducibility) among observers, with similar accuracy compared to the Brugada algorithm. It is of note that the inclusion of steps 1 and 2, differently from the study by Nagi et al.,¹⁵ increased the Sp of the simplified algorithm (100% and 97%, respectively), thus providing results that are comparable to the presence of atrioventricular dissociation^{16,17} and steps 1 and 2 of the Brugada algorithm as reported in the original work.⁶

Not surprisingly, it was not possible to reproduce the high accuracy, Sn, and Sp described by Brugada et al.⁶ as previously reported by other authors.^{4,7, 11,18} One reason may rely on the fact that the evaluators who developed the Brugada algorithm were far more experienced than those in other studies. These findings were confirmed by our study, in which the diagnostic accuracy obtained by cardiologists using the Brugada algorithm was higher than that obtained by physicians who were less experienced in arrhythmia or cardiology (84.6%, 85.8% and 73.7% by groups I, II, and III, respectively). In group III, the two criteria presented similar results in terms of diagnostic accuracy (73.7% using the Brugada algorithm and 72.9% using the simplified algorithm). In addition, the ECG recordings in our study may also differ from those presented in the paper by Brugada et al.,⁶ where no information was obtained about patients showing pre-existing bundle branch block, idiopathic VT, pre-excited SVT, or SVT-A, situations that were not investigated in the present study.^{19,20}

Although a history of structural heart disease (prior myocardial infarction, angina pectoris, or congestive heart failure) has given a high PPV for VT,²¹ no significant increase in accuracy was obtained when the presence of clinical information was added to the analysis using

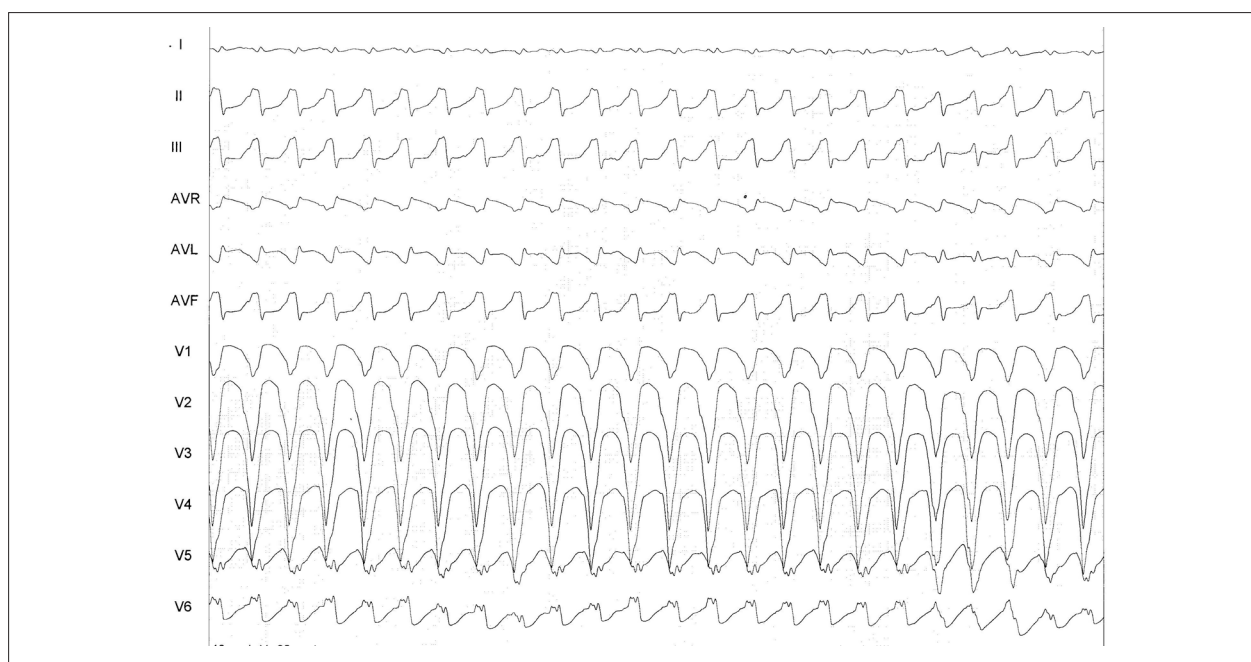


Figure 5 – Example of wide complex tachycardia with diagnostic disagreement – while the simplified algorithm suggests supraventricular tachycardia with aberrant conduction (SVT-A) (step 3), the Brugada algorithm suggests ventricular tachycardia (step 4).

both ECG methods. When comparing the Brugada algorithm according to the presence or absence of clinical information data ($k = 0.566$; 95% CI, 0.5–0.63 and $k = 0.607$, 95% CI, 0.54–0.67, respectively), we observed a slight increase in the diagnosis. One possible explanation is that when clinical information was added to “borderline” ECG recordings by the Brugada analysis, the examiners had a reinforcement for the final diagnosis. This fact was not observed for the simplified algorithm, possibly because the analysis of the proposed interpretation of ECG parameters had a “visual” appeal, not demanding extensive analysis.

Ventricular tachycardia is predominant among patients with WCT.^{8,22} In our study, the prevalence of VT was 68%, while structural heart disease was detected in 87% of patients, confirming the findings in other studies.^{5,21,23} Although the D12V16 and the Brugada algorithms presented similar accuracy for VT diagnosis (rates of 73.8% and 81.4%, respectively), they diverged in terms of Sn and Sp. Therefore, different diagnostic criteria for VT or SVT-A have different diagnostic values. For instance, an evaluator is unlikely to misdiagnose VT using the Brugada algorithm due to its high Sn (87.2%). On the other hand, it is unlikely that VT would be misdiagnosed using the D12V16 algorithm due to its high Sp (85.1%).

The greatest discrepancy was related to Sp of the Brugada method (68.9% in our study vs. 96.5% in the original work published by the authors).⁶ Lau et al.,²² Vereckei et al.,⁸ and Griffith et al.⁴ also showed lower Sp values using the Brugada algorithm (44%, 73.3%, and 67%, respectively) than the values originally reported.

The greater Sn of the Brugada algorithm has important clinical implications in acute management, since it decreases the possibility that patients with VT are treated as having SVT-A, which would lead to deleterious consequences.² On the other hand, the higher PPV (95.8%) of the second step of the D12V16 algorithm could have future implications for clinical practice decision-making and for the development of other discriminatory algorithms to improve diagnostic performance. However, it should be emphasized that when the D12V16 algorithm criteria are not met for VT, it is not possible to conclude that SVT-A is the final diagnosis, due to the relatively low Sn (68.7%) of this new algorithm.

Herbert et al.¹¹ investigated the variability between observers to differentiate VT from SVT-A using the Brugada algorithm in the emergency medicine scenario. A discrepancy of 22% was observed in the diagnostic prevalence. In our study, among the six evaluators, a higher percentage of disagreement was detected with the use of the Brugada algorithm compared with the D12V16 algorithm (60.8% and 30%, respectively). This difference was statistically significant ($p < 0.001$) and no reduction was observed in the presence of clinical information (51.7%, and 30.8% respectively; $p < 0.001$). These results could be explained because D12V16 algorithm has probably a simpler, three-step methodology.

In summary, this study assessed a simple algorithm for the diagnosis of WCT and compared it with the traditional

Brugada algorithm.⁶ Evaluators with distinct experiences performed the analysis with or without clinical information. Both D12V16 and Brugada algorithms had similar accuracy for the differential diagnosis of wide QRS tachycardia. The Brugada algorithm proved more efficient when applied by cardiologists (groups I and II) as compared with the D12V16 algorithm, a difference that was not observed when it was used by emergency medicine resident physicians (group III). Steps 1 and 2 of the simplified algorithm had a high PPV for VT diagnosis. The Sp and agreement between examiners were higher using the D12V16 algorithm. Additionally, the diagnostic accuracy of the two methods did not increase significantly with the availability of clinical information (presence or absence of heart disease).

Limitations

One of the main limitations of the study is that it had conducted in a non-emergency environment and the evaluators had no time restrictions for performing the diagnosis, thus eliminating factors such as stress and quick decisions, which are common situations in the emergency room. The observers had all the leads of the ECGs recordings available and not only the specific ones, e.g. bipolar I-II and precordial V1-V6 leads, when using the simplified algorithm or V1-V6 when using the Brugada algorithm. Although this is the method used in the “real world,” this global vision of the electrocardiogram could influence the differential diagnosis. As the final Sn of the algorithm was 68.7% for VT if all three criteria were negative for VT, the misdiagnosis of VT as SVT-A could lead to a deleterious treatment in the emergency setting if only this algorithm is employed.

The number of examiners in each group was small and each one analyzed each electrocardiogram more than one time. We did not analyze the diagnostic variability between observers of the same groups and between different moments of ECG analysis. This could limit the interpretation of the results.

Additionally, other possible causes of WTC were excluded, such as antidromic pre-excited SVT, ventricular paced rhythm, hyperkalemia or other electrolytic disturbances, toxicity for IA and IC antiarrhythmic drugs, and use/abuse of tricyclic antidepressant medications. We also excluded pediatric WCT patients from the analysis. We did not compare the D12V16 algorithm with other algorithms, such as the Pava criterion²⁴, both Vereckei algorithms,^{8,9} the Bayesian approach,²⁵ and the most recent VT score.¹⁰ External validation of this modified algorithm could bring additional information about the consistence of this algorithm.

Conclusions

This simple three-step D12V16 algorithm demonstrated high Sp and PPV for VT diagnosis and may represent a simple and useful tool to recognize VT in patients with WCT. The algorithm showed similar accuracy compared with the Brugada algorithm when analyzed by less

experienced observers. However, it should be emphasized that when the steps of the D12V16 algorithm are not fulfilled for VT, it is not possible to conclude that SVT-A is the final diagnosis due to the relatively low Sn (68.7%), and thus the risk of “missing” some VT diagnoses. Further studies should be conducted to validate our results.

Author contributions

Conception and design of the research: Santos Neto F, Pisani CF, Darrieux FCC, Cirino CMF, Pérez-Riera AR, Barbosa-Barros R, Scanavacca M; Acquisition of data and Writing of the manuscript: Santos Neto F; Analysis and interpretation of the data: Santos Neto F, Cirino CMF, Santos AM, Scanavacca

M; Critical revision of the manuscript for intellectual content: Santos Neto F, Darrieux FCC, Hachul DT, Scanavacca M.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Simplified Algorithm for Differential Diagnosis of Tachycardias with Wide QRS. Is this the Best Way to Train Young Doctors?

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Short Editorial related to the article: Validation of a Simple Electrocardiographic Algorithm for Detection of Ventricular Tachycardia

To make the correct diagnosis of ventricular tachycardia in an emergency room (ER), with little time for decision-making and based only on the electrocardiogram is a challenge that depends on a lot of preparation by the doctor. Any instrument that facilitates and streamlines this process, especially increasing the degree of accuracy, is also worthy of praise, especially considering that the physician on duty is not always a cardiologist, or even less likely an arrhythmologist, sufficiently trained to make an accurate diagnosis.

An episode of ventricular tachycardia, supraventricular tachycardia (in a patient with a previous conduction disorder or with a conduction aberrancy) and supraventricular tachycardia caused by anomalous bundles may show similar electrocardiographic tracings, which are sometimes very difficult to differentiate, making the medical decision a risk to the patient's life. To make this differentiation possible, several algorithms have been created that use electrocardiographic signals to assist and allow the correct diagnosis to be made and, consequently, to establish the adequate treatment, as in the case of the Brugada algorithm which is widely known (and that in fact is a combination of Brugada and Wellens criteria), as well as Vereckeï and Pava criteria among others. All the created algorithms have sensitivity and specificity (S/E) variables that make them more or less accurate; however, in the same proportion, these algorithms can be simpler, or more complex (depending on the operator's better training and greater time to reach the diagnosis).

The authors of the article "Validation of a Simple Electrocardiographic Algorithm for Detection of Ventricular Tachycardia" aim at obtaining a tool that allows physicians with less training to reach a differential diagnosis in a simpler way and in less time, using a very simplified algorithm, initially developed by Nagi et al. but that was not properly validated, as explained by these authors. The proposal was

to validate the algorithm by comparing more experienced versus less experienced groups of examiners and ECGs with no clinical history and with clinical history. The precise diagnosis of tachycardia was previously evaluated through the electrophysiological study. A significant number of evaluations resulted from this combination, which allowed the statistical analysis of S/E compared with the Brugada algorithm. The final analysis showed that the new algorithm was similar to Brugada's, with a lower rate of conflict between the examiners, showing greater reproducibility. The discussion is precisely in the limitations of the study, because the algorithm was validated only in patients who were not using antiarrhythmic drugs and cases with ventricular pre-excitation were not included either. Both conditions cannot be ruled out in patients who arrive at the ER with tachycardia and a wide QRS interval. It is also careless to consider supraventricular tachycardia in all cases that do not meet the four criteria of this algorithm. In my experience, it is best to confront the various algorithms to reinforce the diagnostic suspicion, a fact that has already been discussed by other authors and we must also consider the simplicity of the Vereckeï's algorithm, which has been widely validated and is easily memorized by the least experienced doctors.

Another limitation is the need for a complete ECG, a test that is not always available in ERs and IUC monitors. In this case, a new and simple algorithm was idealized, allowing good S/E in relation to the most complex algorithms. Unfortunately, there is no algorithm that allows 100% S/E, and I believe we will have to live with these discussions for a long time yet, but, using the clinical criteria associated with the algorithm mastered by the evaluating physician, we can help as much as possible the patients who find themselves in these critical situations.

Keywords

Tachycardia, Emergencies; First Aid; Algorithms; Diagnosis; Algorithms.

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Short Editorial

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Gensini Score and Thrombus Burden Add Predictive Value to the SYNTAX Score in Detecting No-Reflow after Myocardial Infarction

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Abstract

Background: No-reflow after percutaneous coronary intervention is associated with poor prognosis in patients with ST-segment elevation myocardial infarction (STEMI). SYNTAX score is a good predictor of no-reflow.

Objective: We aimed to evaluate whether atherosclerotic burden (Gensini score) and thrombus burden in the culprit coronary artery would improve the ability of the SYNTAX score to detect no-reflow.

Methods: In this prospective cohort study, consecutive patients with STEMI who presented within 12 h of onset of symptoms were selected for this study. No-reflow was defined as TIMI flow < 3 or TIMI flow = 3 but myocardial blush grade < 2. Thrombus burden was quantified according to the TIMI thrombus grade scale (0 to 5).

Results: A total of 481 patients were included (mean age 61 ± 11 years). No-reflow occurred in 32.8%. SYNTAX score (OR=1.05, 95%CI 1.01–1.08, $p < 0.01$), thrombus burden (OR=1.17, 95%CI 1.06–1.31, $p < 0.01$), and Gensini score (OR=1.37, 95%CI 1.13–1.65, $p < 0.01$) were independent predictors of no-reflow. Combined scores had a larger area under the curve than the SYNTAX score alone (0.78 [0.73–0.82] vs 0.73 [0.68–0.78], $p = 0.03$). Analyses of both categorical (0.11 [0.01–0.22], $p = 0.02$), and continuous net reclassification improvement (NRI > 0) (0.54 [0.035–0.73], $p < 0.001$) showed improvement in the predictive ability of no-reflow in the combined model, with integrated discrimination improvement (IDI) of 0.07 (0.04–0.09, $p < 0.001$).

Conclusions: Our findings suggest that, in patients with STEMI undergoing percutaneous coronary intervention, atherosclerotic burden and thrombus burden in the culprit artery add predictive value to the SYNTAX score in detecting the no-reflow phenomenon. (Arq Bras Cardiol. 2021; 116(3):466-472)

Keywords: Percutaneous Coronary Intervention/methods; Myocardial Infarction; Atherosclerosis; Thrombosis; Plaque, Atherosclerotic; Embolization, Therapeutic.

Introduction

Percutaneous coronary intervention (PCI) is the reperfusion strategy of choice for ST-segment elevation myocardial infarction (STEMI).¹ More than to restore the patency of the arterial lumen, the objective of this intervention is to provide blood flow in the coronary microcirculation.² However, in one out of three patients, the microvascular flow remains diminished despite restoration of epicardial coronary artery patency, a phenomenon named no-reflow (NR).^{2,3} The NR is associated with an increased incidence of heart failure, cardiogenic shock, and death.³⁻⁵

A sizeable number of markers for microvascular obstruction have been described, particularly age and time to reperfusion.^{6,7} More recently, it has been shown that anatomic complexity for PCI, as estimated by the SYNTAX score, may also relate to a higher risk for NR.⁸⁻¹⁰ As NR occurs more frequently than the above-mentioned markers, it is possible that other clinically relevant markers exist. In this context, it is hypothetically plausible that atherosclerotic and thrombotic burden may add predictive value to the SYNTAX score, age, and time to reperfusion in the prediction of NR. The present study was therefore designed to test this hypothesis.

Methods

Sample selection

This study was based on a subanalysis of the Brasilia Heart Study (BHS), whose design is described elsewhere.¹¹ Briefly, the BHS is a single-center, prospective cohort

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Original Article

study of consecutive patients with STEMI who presented within 24 h of onset of symptoms. STEMI was defined as follows: 1) ST-segment elevation of at least 1 mm in the frontal plane or 2 mm in the horizontal plane in two contiguous leads, or new left bundle branch block on electrocardiogram; 2) positive myocardial necrosis marker, defined as troponin I >0.04 ng/mL and CK-MB >25 U/L, corresponding to values above the 99th percentile. Patients undergoing PCI within 12 h of STEMI were eligible for the present study. Written informed consent was obtained from all participants, and the study was approved by the research ethics committee of the institution. All procedures were in accordance with the ethical standards of the institutional committee on human experimentation and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Angiographic analysis

All angiograms were reviewed by two experienced interventional cardiologists who independently interpreted the images and evaluated the following parameters:

1) coronary flow: TIMI flow grade;¹² 2) myocardial perfusion: myocardial blush grade (MBG);¹³ 3) thrombus burden: TIMI thrombus grade scale;¹⁴ 4) angiographic SYNTAX score⁸ and modified Gensini score.¹⁵ The scores were obtained from the diagnostic angiogram before any intervention. The two cardiologists agreed on the interpretation of findings, with an intraobserver and interobserver variability of 5%.

NR was defined as a TIMI flow grade < 3 or TIMI flow grade = 3 but MBG < 2 at coronary angiography performed after PCI of the STEMI-related artery.

Statistical analysis

Quantitative data were expressed as mean and standard deviation (SD). Groups were compared using Student's *t* test for parametric continuous variables or the Mann-Whitney test for nonparametric continuous variables, and the chi-square test was used for categorical variables. Binary logistic regression was used to determine predictors of the NR phenomenon in models unadjusted (model 1) and adjusted (model 2) for GRACE score and reperfusion

Table 1 – Clinical and biochemical characteristics of 481 patients undergoing percutaneous coronary intervention for ST-segment elevation myocardial infarction (STEMI) who showed optimal reperfusion or no-reflow after the procedure

Parametric variables	Total (n = 481)	Optimal reperfusion (n = 323)	No-reflow (n = 158)	P-value*
	mean ± SD	mean ± SD	mean ± SD	
Age (years)	61±11	61±11	61±12	0.64
BMI (kg.m ⁻²)	27.0±4.2	26.8±3.9	27.3±4.7	0.32
GRACE on hospital admission	136±26	135±27	137±24	0.46
First-day total cholesterol (mg.mL ⁻¹)	192±48	192±45	191±53	0.83
First-day HDL-c (mg.mL ⁻¹)	40±11	38±10	38±11	0.63
HbA1c (%)	6.5±1.8	6.5±1.8	6.4±1.7	0.64
Non-parametric variables	Median (Q1 - Q3)	Median (Q1 - Q3)	Median (Q1 - Q3)	P-value†
Reperfusion time	111 (60 - 210)	96 (60 - 206)	120 (60 - 239)	0.42
First-day LDL-c (mg.mL ⁻¹)	117 (93 - 143)	117 (97 - 145)	118 (94 - 141)	0.50
First-day triglycerides (mg.mL ⁻¹)	134 (87 - 207)	135 (90 - 215)	133 (84 - 195)	0.11
Categorical variables	f (%)	f (%)	f (%)	P-value*
Male, n (%)	359 (75)	235 (73)	124 (78)	0.34
DM, n (%)	148 (31)	94 (29)	54 (34)	0.34
Hypertension, n (%)	279 (58)	187 (58)	92 (58)	0.97
Stroke, n (%)	21 (4)	11 (3)	10 (6)	0.24
Smoking, n (%)	183 (38)	127 (39)	56 (35)	0.35
Physical inactivity, n (%)	261 (54)	179 (55)	82 (52)	0.37
Previous PCI, n (%)	26 (5)	15 (5)	11 (7)	0.35
CABG, n (%)	4 (0.8)	3 (0.9)	1 (0.6)	0.86
Killip >1, n (%)	52 (11)	31 (10)	21 (13.2)	0.44

SD: standard deviation; Q1: first quartile; Q3: third quartile. CABG: coronary artery bypass grafting; GRACE: Global Registry of Acute Coronary Events; DM: type 2 diabetes mellitus; PCI: percutaneous coronary intervention; BMI: body mass index; HbA1C: glycosylated hemoglobin; LDL: low-density lipoprotein; HDL: high-density lipoprotein. * unpaired Student's *t* test; † Non-parametric Mann-Whitney test; ‡ Chi-squared test.

time (time between symptom onset and reperfusion) after reperfusion. Receiver operating characteristic (ROC) curve analysis was performed to determine the predictive ability of the models. Net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used to determine improvements with the addition of new predictors. Statistical analysis was performed using SPSS for Mac version 23.0 (SPSS Inc., Chicago, IL, USA), and R for Mac version 3.4.2. A p-value <0.05 was considered statistically significant.

Results

A total of 481 patients undergoing PCI in the acute phase of STEMI were included in the present study. Mean patient age was 61 (SD 11) years, and 74.6% were men, 58.0% had hypertension, 54.2% were physically inactive, 38.0% were smokers, and 30.7% had diabetes.

NR occurred in 32.8% of the patients (n=158), who were then compared to those who had optimal reperfusion (n=323). Clinical and biochemical characteristics of both groups are described in Table 1.

Gensini score, Gensini score of the culprit artery, SYNTAX score, and thrombus burden were significantly higher in the NR group than in the optimal reperfusion group (Table 2). Both unadjusted and adjusted logistic regression models showed that SYNTAX score, Gensini score, and thrombus burden were independent predictors of NR (Table 3). ROC curve analysis showed that the model with combined scores had a larger area under the ROC curve than the model with the SYNTAX score alone (0.778 [0.733 - 0.823] vs. 0.737 [0.688 - 0.786]) (Figure 1).

NRI and stratification of NR between the SYNTAX score alone and combined SYNTAX, Gensini, and thrombus burden scores are shown in Table 4. Both categorical

Table 2 – Angiographic parameters of 481 patients undergoing percutaneous coronary intervention for ST-segment elevation myocardial infarction (STEMI)

Parameters	n = 481	Optimal reperfusion n = 323	No-reflow n = 158	p
Gensini score	100±70	82±62	139±69	<0.001
Gensini score – culprit artery	62±49	48±38	87±56	<0.001
SYNTAX score	12±10	9±8	17±10	<0.001
Thrombus burden – culprit artery, n (%)	181 (37.6)	89 (27.5)	92 (58.2)	<0.001
TIMI thrombus grade scale, n (%)				<0.001
0	300 (63)	234 (72)	66 (42)	
1	9 (1.9)	8 (2.5)	1 (0.6)	
2	21 (4.4)	13 (4)	8 (5)	
3	18 (3.7)	14 (4.3)	4 (2.5)	
4	18 (3.7)	11 (3.4)	7 (4.4)	
5	115 (24)	43 (13.3)	72 (46)	

Values are expressed as mean ± standard deviation. TIMI: thrombolysis in myocardial infarction.

Table 3 – Logistic regression model of the SYNTAX, Gensini, and thrombus burden scores as predictors of the no-reflow phenomenon

Models	OR (95%CI)	p
Model 1 (unadjusted)		
Age	1.02 (1.00-1.03)	0.037
Reperfusion time	1.00 (1.00-1.01)	0.154
SYNTAX score	1.10 (1.07-1.12)	<0.001
Thrombus burden	1.38 (1.26-1.51)	<0.001
Gensini score	1.76 (1.50-2.07)	<0.001
Model 2 (multivariate)*		
Age†	1.01 (0.98-1.02)	0.325
Reperfusion time	0.98 (0.99-1.00)	0.645
SYNTAX score	1.05 (1.01-1.08)	<0.01
Thrombus burden	1.17 (1.06-1.31)	<0.01
Gensini score	1.37 (1.13-1.65)	<0.01

CI: confidence interval; OR: odds ratio. All models were adjusted for GRACE score and reperfusion time (time between symptom onset and reperfusion).

* adjusted for GRACE score; † not including GRACE score.

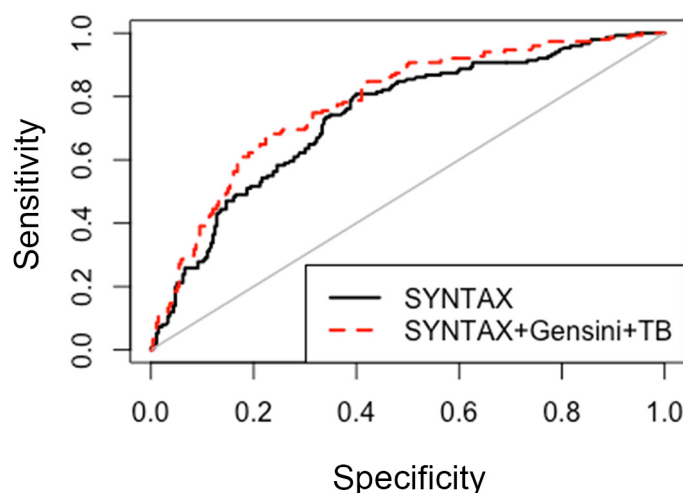


Figure 1 – Comparison of ROC curves between combined SYNTAX, Gensini, and thrombus burden (TB) scores and the SYNTAX score alone.

Table 4 – Net reclassification improvement (NRI) and stratification of no-reflow between combined SYNTAX, Gensini, and thrombus burden scores and the SYNTAX score alone

SYNTAX score alone	Combined scores			Reclassification
	Low	Intermediate	High	
Low	301	26	1	8%
Intermediate	23	22	34	72%
High	2	9	6	65%

and continuous NRI analyses showed improvement in the predictive ability of NR in the combined model, which was also indicated by the integrated discrimination improvement (IDI) (Table 5).

Discussion

Among the main findings of this study, we found that (1) SYNTAX score, Gensini score, and thrombus burden were all independent predictors of NR; and (2) the combination of atherosclerotic burden and thrombus burden scores with the SYNTAX score increased the predictive value of the SYNTAX score in detecting the NR phenomenon.

Although the SYNTAX score is a good predictor of microvascular dysfunction, total atherosclerotic burden is not considered in the algorithm, as it excludes occlusive lesions with less than 50% stenosis. Furthermore, thrombotic burden is also not considered in the SYNTAX algorithm, as it only assigns a relatively small score for the presence or absence of thrombus.⁸ Conversely, Gensini score is very representative of total atherosclerotic burden, because it considers lesions as from 25% luminal stenosis,^{15,16} and is significantly associated with average plaque burden and plaque area as measured by intracoronary ultrasound.¹⁷ High Gensini scores may indicate multivessel disease and an increase in microvascular resistance, both of which are factors associated with NR.^{5,10,18}

In the present study, Gensini score was an independent predictor of NR. Modolo et al.¹⁹ showed that total Gensini score and Gensini score of the culprit artery were higher in individuals with NR than in individuals with optimal reperfusion.¹⁹ However, the severity of luminal stenosis is not the only angiographic predictor of microvascular dysfunction. In fact, plaque morphological changes such as lipid-rich content, large necrotic core, and large amount of attenuated plaque are also strong predictors of NR,^{20,21} suggesting that altered plaque volume and content cause impaired autoregulation and local release of vasoconstrictors, boosting thrombus formation, microembolization of arterial beds and microvascular obstruction.

In the present study, 58.5% of patients in the NR group had thrombus in the culprit artery; 50.4% of these with large thrombus burden (grades 4 and 5 of the TIMI thrombus grade scale), a possible reason for the association with NR. In a large cohort of patients with STEMI undergoing PCI, large thrombus burden was associated with NR (4.0 vs 0.5, $p < 0.001$) and distal embolization (17.3 vs 3.4, $p < 0.001$).²²

The SYNTAX score was significantly higher in the NR group than in the optimal reperfusion group (17 ± 10 vs 9 ± 8) and was an independent predictor of NR. In a previous study, the SYNTAX score was a predictor of NR, and a SYNTAX score > 21 doubled the risk of developing NR.⁹ Total occlusion of the STEMI-related artery, site of

Table 5 – Continuous and categorical net reclassification improvement (NRI), integrated discrimination improvement (IDI), and predictive value of no-reflow between combined SYNTAX, Gensini, and thrombus burden scores and the SYNTAX score alone

Variables	NRI	95%CI	p
Continuous	0.54	0.351-0.7347	<0.001
Categorical	0.12	0.0119-0.2223	<0.02
IDI	0.066	0.040-0.092	<0.001

CI: confidence interval.

occlusion (left main or left anterior descending coronary artery), presence of thrombus, longer lesions, bifurcation lesions and multivessel disease are factors associated with increased SYNTAX scores and may explain the association with NR.^{9,10,23}

In the present study, the NR phenomenon occurred in 32.8% of cases, with TIMI flow <3 or TIMI flow =3 but MBG <2 as angiographic criteria. The incidence of NR is much higher in STEMI than in elective PCI, being reported in 30 to 50% of patients undergoing primary PCI for STEMI.³ Rezkalla et al.,³ investigating NR in patients with STEMI, found a prevalence of 32% as assessed by TIMI and of 52% by MBG.

Age is an important marker of NR. Older patients have higher plaque burden, diffuse coronary atherosclerosis and severe vascular calcification, which may contribute to microvascular dysfunction.^{24,25} Zhou et al.⁶ identified that age > 65 years (OR= 1.470, 95%CI 1.460-1.490, p=0.007), was an independent predictor of NR.⁶ In our study, in univariate analysis, age predicted NR, but in multivariate analysis this relationship was not maintained.

Delayed reperfusion is associated with NR. Previous studies have shown that patients with longer reperfusion time (> 6 h) show a significant increase in NR.^{6,7} However, a study using a shorter cut-off point (< 6 h) from symptom onset did not indicate delayed presentation as an independent predictor of NR.²³ In our study, reperfusion time was 2.94 h in the NR group and 2.5 h in the optimal reperfusion group. Multivariate analysis adjusted for GRACE score did not show reperfusion time as a predictor of NR.

The pathophysiology of the NR phenomenon is multifactorial and involves individual susceptibility, ischemia-related injury, reperfusion-related injury, and distal embolization.²⁶ During PCI, in the setting of STEMI, distal embolization of thrombus and atherosclerotic plaque components are important mechanisms involved in the pathogenesis of NR.^{27,28} The released atherothrombotic material causes mechanical obstruction, vasoconstriction due to the release of serotonin, thromboxane A2, and endothelin, and endothelial dysfunction due to increased expression of tumor necrosis factor alpha (TNFα).²⁸⁻³⁰ Likewise, the release of platelet- and endothelial-derived microparticles is associated with reduced myocardial perfusion as assessed by MBG and with larger thrombus burden.³¹ The burden of neutrophil extracellular traps may propagate thrombosis and inflammation distally into the culprit artery, contributing to myocyte death.^{32,33}

A limitation of this study is that it represents the experience of a single center. Also, coronary angiography has limited ability to estimate both thrombotic and atherosclerotic plaque burden compared with intracoronary ultrasound and optical coherence tomography.

Conclusion

Atherosclerotic burden assessed by Gensini score and thrombus burden in the culprit artery add predictive value to the SYNTAX score in detecting the NR phenomenon after PCI in patients with STEMI.

Author contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Matos L, Carvalho LS, Modolo R, Santos S, Silva JCQ, Almeida OLR, Sposito AC; Statistical analysis: Matos L, Carvalho LS, Modolo R, Almeida OLR, Sposito AC; Obtaining financing: Silva JCQ, Sposito AC; Writing of the manuscript: Matos L, Carvalho LS, Sposito AC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the FEPECS/SES-DF under the protocol number 47145515.6.0000.5553. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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Angiographic Scores in Prediction of No-Reflow, Myocardial Injury May not end with Reperfusion

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Short Editorial related to the article: Gensini Score and Thrombus Burden Add Predictive Value to the SYNTAX Score in Detecting No-Reflow after Myocardial Infarction

The ST segment elevation infarction (STEMI) is usually precipitated by the rupture or erosion of an atherosclerotic plaque and the consequent formation of an occlusive thrombus. Early percutaneous coronary intervention is the treatment of choice for providing a more complete revascularization and less bleeding complications when compared to fibrinolysis.^{1,2}

In the last decades, we observed a substantial development in the pharmacological and invasive treatments of STEMI, which significantly reduced early mortality. Several variables affect clinical outcomes, including patient age, time to reperfusion, angiographic complexity and the occurrence or not of the no-reflow (NR) phenomenon during percutaneous intervention.^{3,4} NR is defined by inadequate myocardial perfusion in a given territory, in the absence of mechanical obstruction of the epicardial coronary⁵ and is associated with a worse clinical prognosis.^{6,7}

In this edition, the "Arquivos Brasileiros de Cardiologia" publish the article "Gensini Score and Thrombus Burden Add Predictive Value to the SYNTAX Score in Detecting No-Reflow after Myocardial Infarction", the authors evaluated the angiography of 481 consecutive patients admitted by STEMI and calculated the SYNTAX and modified Gensini scores, in addition to assessing thrombotic burden objectively. A better accuracy of the prediction of the NR phenomenon was found when the combination of the three scores was used.⁸

The Gensini score was first described in 1975 and takes into account 3 parameters for each coronary lesion: severity of the obstruction, multiplied by a factor according to the importance of the region irrigated by the artery and adjusted by the presence of collaterals;⁹ includes stenoses less than 25% and is, therefore, more sensitive to partial obstructions than SYNTAX SCORE. The objective quantification of

thrombotic load is determined by the TIMI scale from 0 to 5, where 0 is the absence of a thrombus and 5 is the presence of an occlusive thrombus.¹⁰

The relationship of these angiographic scores to the presence of NR phenomenon makes physiopathological sense, because although it is not fully clarified, the NR phenomenon in patients undergoing primary percutaneous intervention has distal microembolization as one of its causes,¹¹ which depends on the angiographic variables studied by the authors. In the published study, no data were reported about the procedures (thrombus aspiration, stents, post-dilation), medications used and reversibility of the phenomenon that also significantly impact the angiographic and clinical prognosis.

The act of predicting a potentially catastrophic phenomenon is important when it impacts on changing strategy before it occurs. The DEFER-STEMI study, published in 2014, touched precisely on this point: a proof-of-concept trial that assessed the impact of delayed-stent (with the artery already reperfused by balloon or thrombus aspiration) in order to reduce the incidence of NR and the size of the infarction, assessed by magnetic resonance imaging - the rationale is that delayed stent may allow time for the action of antithrombotic drugs, reduced thrombus burden and consequently less NR and smaller infarcted area. In fact, in this study, there was a significant reduction in NR (from 14% to 2% in the stent-delayed group) and an improvement in the myocardial salvage rate in 6 months.¹² Later, in 2017, a meta-analysis brought together 9 studies and the reduction in NR was not observed, however, an improvement in long-term ventricular function in the delayed stent group was pointed out.¹³

Other strategies such as the use of intracoronary drugs (adenosine, calcium channel blockers and nitroprusside) and glycoprotein IIb/IIIa inhibitors have shown some benefit in the prevention and treatment of NR and need further studies.¹⁴

The NR phenomenon is the greatest challenge of primary reperfusion and despite efforts; knowledge has evolved little in the treatment or prevention of this condition. Angiographic scores, which make the assessment of cineangiocoronariography more objective, contribute to the discrimination of patients with a worse prognosis, particularly when the association of classic scores is used (SYNTAX, Gensini, Thrombotic load), as demonstrated in this article. Recognizing these patients can lead to optimization of treatment and improvement of outcomes.

Keywords

Percutaneous Coronary Intervention/methods; Myocardial Infarction; Atherosclerosis; Plaque Atherosclerotic; Embolization Therapeutic.

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Arterial Stiffness Changes in Severe Aortic Stenosis Patients Submitted to Valve Replacement Surgery

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Abstract

Background: Little is known about the impact of severe aortic stenosis (AS) in aortic stiffness and if there is any change after removing AS barrier with aortic valve replacement (AVR) surgery.

Objective: To estimate carotid-femoral pulse wave velocity (PWV) changes after AVR surgery and to define PWV predictors in severe AS patients.

Methods: Single-center retrospective cohort, including patients with severe AS who underwent AVR surgery with bioprostheses, between February 2017 and January 2019 and performed PWV measurements (Complior®) before and after the procedure (2±1 months). Before and after AVR, PWV values were compared through paired tests. The associations of PWV with clinical data were studied and linear regression models were applied to estimate pre and postoperative PWV independent predictors. The significance level was set at 5%.

Results: We included 150 patients in the sample, with mean age of 72±8 years, and 51% being males. We found a statistically significant increase in PWV values after surgery (9.0±2.1 m/s vs. 9.9±2.2, $p<0.001$, before and after AVR, respectively) and an inverse association with AS severity variables. In the linear regression model, age and systolic blood pressure (SBP) were established as independent predictors of higher pre- and postoperative PWV, while higher mean valvular gradient emerged as a determinant of lower pre-AVR PWV.

Conclusion: We documented an inverse correlation of arterial stiffness with the severity of AS in patients with AS, and a significant increase in PWV values after AVR surgery. Advanced age and higher SBP were associated with higher PWV values, although arterial function measurements were within the normal range. (Arq Bras Cardiol. 2021; 116(3):475-482)

Keywords: Aortic Valve/surgery; Aortic Valve Stenosis/surgery; Aortic Valve, Replacement /methods; Pulse Wave Analysis.

Introduction

Degenerative aortic stenosis (AS) is the most prevalent valvular heart disease (VHD) in developed countries and the world's most commonly acquired VHD, being moderate or severe in 5% of patients older than 75 years in the USA.¹ The gold standard treatment for its severe symptomatic form is Aortic valve replacement (AVR).²⁻⁴

The degenerative process of the aortic valve (AV), which results in AS, has pathophysiological changes that are similar to the atherosclerotic process responsible for increased arterial stiffness.⁵ The scientific community, therefore, is led to postulate that, in AS, some degree of vascular dysfunction and consequently arterial stiffness could also be present.⁶

Aging also contributes to vascular stiffening, increasing aortic pressure. Aortic pulse wave velocity (PWV) is the gold standard, non-invasive, and most reproducible method to assess arterial stiffness.⁷ Essentially, it evaluates aortic elastic recoil capacity, which is diminished in a stiffer aorta, translating into a higher PWV value.⁸⁻¹⁰ So, in an AS patient, we expect to find a higher preoperative PWV, that may be recovered after AVR. However, some studies have shown that this association may not be linear,¹¹ meaning that even after the procedure that relieves valvular obstruction, a high PWV measurement may be seen (or even higher than the pre-intervention assessment), representing an increase in vascular load.¹²

There is a strong association between a higher PWV and systolic hypertension, as well as other cardiovascular (CV) risk factors and atherosclerotic disease.^{13,14} PWV has also been suggested to predict fatal and nonfatal CV events, such as stroke or aortic and coronary syndromes.^{8,9,15,16}

There is conflicting evidence regarding arterial function changes after AVR, and whether PWV can be a marker of AS severity or not. In this setting, this study aimed to clarify this association.

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Objective

The main goal of this study was to evaluate arterial stiffness before and after AVR surgery in patients with severe AS, using a PWV measurement equipment. We also aimed to identify the predictors of pre and postoperative PWV results in these patients.

Methods

Study Design and Patients

Single-center retrospective study, including 150 patients with severe AS who underwent AVR surgery with bioprostheses between February 2017 and January 2019, with pre and postoperative PWV measurements. Patients with concomitant moderate or severe aortic regurgitation or multiple procedures were excluded.

Data Collection and Variables

Preoperative, surgical, and postoperative data were collected from medical records and databases. Regarding preoperative variables, besides PWV values, we also collected data on blood pressure, demographic information, cardiovascular risk factors, ongoing medical therapy, functional status, symptoms, and transthoracic echocardiogram. Cross-clamp (XCT) and cardiopulmonary bypass time (CPBT), aortic valve disease etiology, and type of prosthesis were the main surgical variables. Follow-up variables were the results of transthoracic echocardiogram (mean at 3.9 ± 1.6 months of follow-up) and PWV evaluation.

The local ethics committee approved this study, and all data were anonymized for analysis.

PWV Measurement

A noninvasive method (Complior® Analyse) was used to evaluate arterial stiffness through carotid-femoral PWV before and after AVR surgery. After a few minutes in supine resting position to stabilize heart rate and blood pressure, the blood pressure was assessed using a standard sphygmomanometer. Carotid to femoral distance was measured using a metric tape, and data were input in a specific software. Femoral and carotid sensors were held until the software reached stabilized lines and the best quality of signal (above 90%). Each patient was submitted to at least two PWV measurements in each session. These measurements were done at patients' admission to the Cardiothoracic Surgery Department on the day before or on the same day of the surgery. The postoperative evaluation occurred on average 2.2 ± 1.4 months after surgery.

Statistical Analysis

The distribution of continuous data was verified through visual analysis of the histograms and confirmed by Shapiro Wilk test. Continuous variables are presented as mean and standard deviation. Categorical variables are depicted in absolute and relative frequencies. Paired samples *t* test was used to compare continuous variables at two distinct

moments. Correlations between PWV and other continuous variables were assessed through Pearson correlation test. PWV values were compared between groups using independent *t* test. A multivariable linear regression model was built to estimate PWV predictors based on clinical variables relevant to arterial stiffness evaluation. The regression's assumptions were checked, residuals were normally distributed and the independent variables were not highly correlated. A significance level of 5% was used. Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 24 and the R language environment version 3.6 (R Core Team - 2018. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <https://www.R-project.org/>. Frank E Harrell Jr - 2019. rms: Regression Modeling Strategies. R package version 5.1-3.1).

Results

Sample

Sample characterization is depicted in Table 1. Mean age of subjects was 72 ± 8 years, and 51% of them were males. Arterial hypertension was present in 125 patients (83%), dyslipidemia in 114 (76%), diabetes in 52 (35%), and history of smoking in 36 (24%). Forty (27%) patients were admitted with New York Heart Association (NYHA) functional class $\geq$ III. Most patients (91%) were on anti-hypertensive drugs at admission.

During surgery, 12% of patients were confirmed for congenital etiology (Table 2).

Table 1 – Baseline characteristics

Variable	n=150
Age, in years, mean (SD)	72.5 (7.6)
Male sex, n (%)	77 (51.3)
NYHA $\geq$ III, n (%)	40 (26.9)
Hypertension, n (%)	125 (83.3)
Currently on anti-hypertensive drugs (%)	136 (90.7)
Diabetes, n (%)	52 (34.9)
Dyslipidemia, n (%)	114 (76.0)
History of smoking, n (%)	36 (24.0)
Body mass index, kg/m ² , mean (SD)	28.6 (4.3)
Obesity (BMI ≥ 30.00 kg/m ²), n (%)	55 (36.7)
Coronary artery disease, n (%)	19 (12.7)
Extracardiac arteriopathy, n (%)	22 (14.7)
Chronic kidney disease (CC < 85 ml/min), n (%)	87 (58.0)
Creatinine Clearance (CC), ml/min, mean (SD)	83.7 (29.7)

BMI: body mass index; min: minute; NYHA: New York Heart Association; SD: standard deviation. Extracardiac arteriopathy was considered if the patient had claudication, carotid occlusion or $> 50\%$ stenosis, amputation due to arterial disease, past or planned intervention on the abdominal aorta, limb arteries or carotids, or history of stroke. Coronary artery disease was defined when patients had undergone percutaneous coronary intervention in the past, or coronary stenosis $> 50\%$, but without indication for surgery.

Table 2 – Perioperative data

Variable	n=150
Aortic valve etiology, n (%)	
Degenerative	132 (88.0)
Congenital	18 (12.0)
CPB time, minutes, mean (SD)	78 (26)
Aortic clamp time, minutes, mean (SD)	57 (20)

CPB: cardiopulmonary bypass; SD: standard deviation.

Pre and Postoperative PWV

A significant postoperative increase in PWV values was observed, ranging from 9.0 ± 2.1 m/s to 9.9 ± 2.2 m/s after AVR surgery ($p < 0.001$, Figure 1A).

Follow-up Data

Systolic blood pressure (SBP), mean aortic valve gradient (MVG) and aortic valve area (AVA) values before and after AVR surgery are represented in Figure 1 (Panels B, C and D, respectively).

PWV Associations

Figure 2 depicts the univariate analysis considering PWV associations with potential predictors. Preoperative and postoperative PWV had positive correlations with age, SBP and mean blood pressure (MBP), but inversely associated with aortic stenosis severity variables. We found no differences in PWV according to gender, arterial hypertension, diabetes, smoking, or bicuspid AV subgroups.

In the multivariable linear regression model, age and SBP were independent predictors of higher preoperative PWV, while higher MVG was a predictor of lower preoperative PWV (Table 3 and Figure 3). Age and SBP were considered independent predictors of higher postoperative PWV (Table 4 and Figure 4).

Discussion

This retrospective study showed an inverse correlation of arterial stiffness with severity of AS and a significant increase in PWV values after AVR surgery in patients with severe AS. Advanced age and higher SBP were associated with higher PWV values, although arterial function measurements were within the normal range.

PWV reflects arterial stiffening due to loss of aortic functional elastic properties. Arterial stiffness is one of the first manifestations of reversible structural damage to the vessel wall, and PWV is considered a technique with clinical applicability both to identify and stratify cardiovascular disease.^{8,16}

Assessing the impact of degenerative AS on the arterial tree remains a challenge, as the mechanisms underlying the interaction of vascular and valvular function remain mostly unknown.¹⁷

Liu et al.⁵ showed the association of increased PWV with higher calcium score in the AV.⁵ These results suggest that calcium deposition is an important pathway in the degenerative process of the aortic valve and wall. In addition, they showed an association between increased PWV and AV pressure gradient assessed by echocardiography. Similar pathophysiological changes are probably shared between AV degeneration and large arteries stiffening. Korkmaz et al.¹⁸ estimated arterial stiffening using the cardio-ankle vascular index and found higher arterial stiffness in patients with aortic valve sclerosis,¹⁸ suggesting that AV degeneration and large arteries stiffening could share similar pathophysiological changes. Indeed, Emir Cantuk et al.¹¹ reported a significant association between AS severity and increased PWV.¹¹ Contrarily, our study shows an inverse correlation between AV gradients and preoperative PWV. This might partially be explained by the upstream obstruction that may influence measurements of arterial properties, masking the real effects of vascular load on the aorta. El-Chilali et al.,⁶ who studied older patients (>70 years old) with severe AS and measured PWV invasively, observed the same: an inverse correlation between MVG and PWV.⁶ This hypothesis is strengthened by the increase in PWV that we found after AVR surgery.

Only a limited number of studies have evaluated aortic vascular function in patients with severe AS after intervention so far.^{11,19,20} Canturk et al.¹¹ did not find significant differences in PWV after surgery.¹¹ On the other hand, Nemes et al.²⁰ demonstrated a vascular function improvement one year after AVR.²⁰ In our study, PWV increased significantly after AVR surgery. Some mechanisms are considered to possibly explain this result: the relief of valvular obstruction after AVR leads the arterial tree to operate at a higher-pressure level, increasing the vascular load. In fact, Yotti et al.¹⁹ showed that the relief of the outflow obstruction immediately raises arterial pressures and vascular impedance, inducing a stiffer vascular behavior.¹⁹ Overall, these findings are reflected in clinical practice, since it is common to initiate anti-hypertensive drugs after AS correction, either by transcatheter aortic valve implantation (TAVI) or surgery.^{19,21,22} Another explanation, stated by Barbetseas,¹² suggests that the increase in arterial stiffness after AVR surgery occurs due to aortic wall injury and vasa vasorum destruction, as well as aortic wall fiber composition alteration, resulting in aortic stiffening. However, we should reinforce that this decrease in aortic distensibility was evaluated one week after AVR, whereas six months after AVR, the aortic function improved, reaching levels similar to preoperative ones.¹² It may represent a transient effect described by the authors as “aortic root stunning”.²³

A study that compared TAVI and AVR showed significant changes in PWV only in surgical patients, suggesting that, in TAVI patients, the elastic properties are maintained because there is no surgical manipulation.²⁴

In our study, PWV was also found to be significantly associated with age, which was considered an independent predictor of higher PWV values. PWV alteration in the elderly is already well established in the literature.^{8,17,25} Studies have shown an increase in PWV with aging probably related to aortic dilation and stiffening, since impedance increases and arterial compliance decreases with aging.^{8,26} Our study supports these

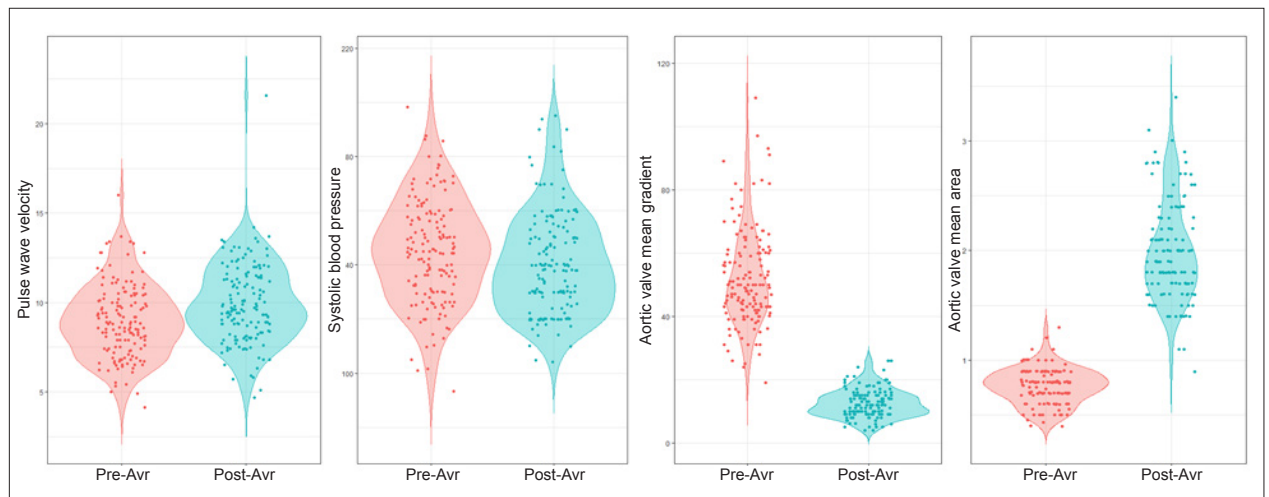


Figure 1 – Violin plots for pre- (red) and post- (blue) operative values of pulse wave velocity (A), systolic blood pressure (B), aortic valve mean gradient (C) and aortic valve area (D).

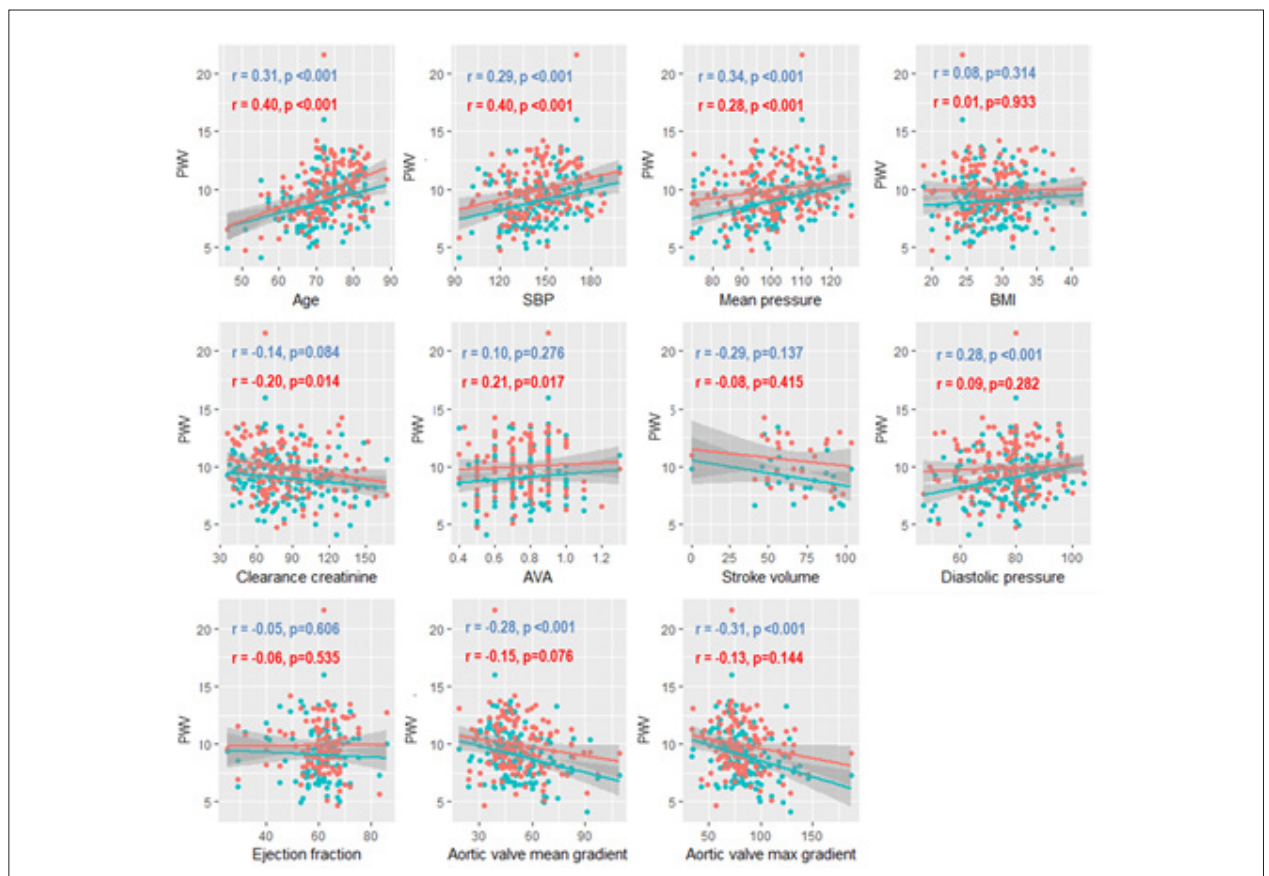


Figure 2 – Scatter plots for pre- (blue) and post- (red) operative PWV relationships with age, SBP: systolic blood pressure, mean pressure, BMI: body mass index, clearance creatinine, AVA: aortic valve area, stroke volume, diastolic pressure, ejection fraction, aortic mean valve gradient and aortic valve maximum gradient.

Table 3 – Summary of the multivariable regression analysis (dependent variable: preoperative PWV)

Variable	β	SE	b	p
Intercept	0.593	2.576	0.23	0.818
Systolic blood pressure	0.020	0.008	2.42	0.017
Diabetes	0.428	0.344	1.24	0.215
Clearance creatinine	-0.001	0.007	-0.14	0.889
Coronary artery disease	0.531	0.498	1.07	0.288
BMI	0.059	0.040	1.46	0.147
Age	0.070	0.025	2.87	0.004
Sex	0.244	0.336	0.73	0.469
MVG	-0.029	0.011	-2.75	0.007
Bicuspid aortic valve	-0.299	0.498	-0.60	0.549

BMI: body mass index; β : unstandardized regression coefficient; b: standardized coefficient; MVG: mean valve gradient; SE: standard error of the coefficient.

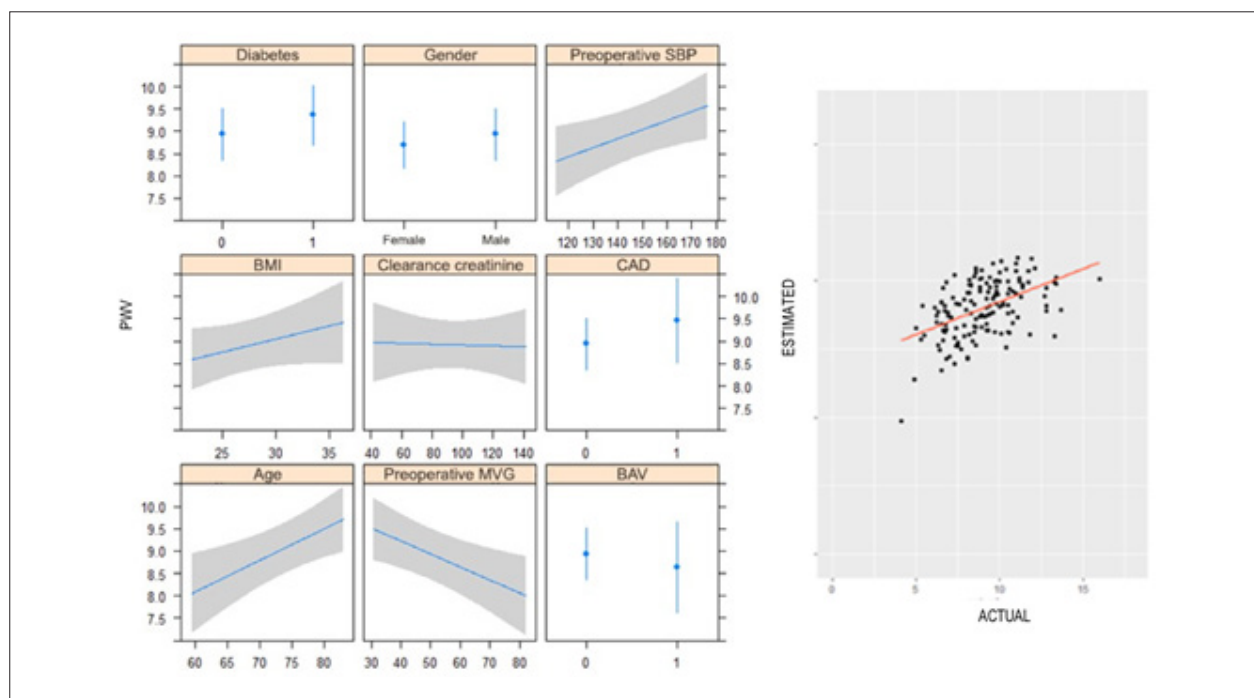


Figure 3 – Multivariable linear regression model of preoperative PWV and estimated versus actual values. BAV: bicuspid aortic valve; BMI: Body mass; CAD: coronary artery disease; MVG: mean valve gradient; SBP: systolic blood pressure.

results, with age proven to be strongly correlated with both pre- and postoperative PWV.

Systemic hypertension was also shown to be a predictor of increased PWV^{9,27} which is in line with our results as higher SBP was associated with higher PWV. Since over 80% of our sample had systemic hypertension, we did not find substantial differences between patients with and without this risk factor, but we recognize that PWV has been widely used for risk stratification purposes as an independent risk factor for all-cause and CV mortality.^{27,28}

Considering that atherosclerosis is commonly associated with arterial aging and coronary artery disease (CAD), it would be expected that patients with CAD had increased PWV.^{29,30} In fact, our results showed a significantly higher post-AVR PWV in patients with CAD in comparison with non-CAD patients. However, this difference was absent in pre-AVR PWV, which supports the hypothesis of a masking effect in the presence of AS, blunting the manifestation of aortic stiffening induced by CAD.

Table 4 – Summary of the multivariable regression analysis (dependent variable: postoperative PWV)

Variable	β	SE	b	p
Intercept	-2.706	2.391	-1.13	0.260
Systolic blood pressure	0.037	0.009	4.11	<0.001
Diabetes	0.448	0.352	1.27	0.205
Coronary artery disease	0.837	0.508	1.65	0.102
BMI	0.023	0.040	0.58	0.564
Age	0.097	0.023	4.13	<0.001
Sex	0.287	0.351	0.82	0.415
MVG	-0.056	0.038	-1.46	0.146

BMI: body mass index; β : unstandardized regression coefficient; b: standardized coefficient; MVG: mean valve gradient; SE: standard error of the coefficient.

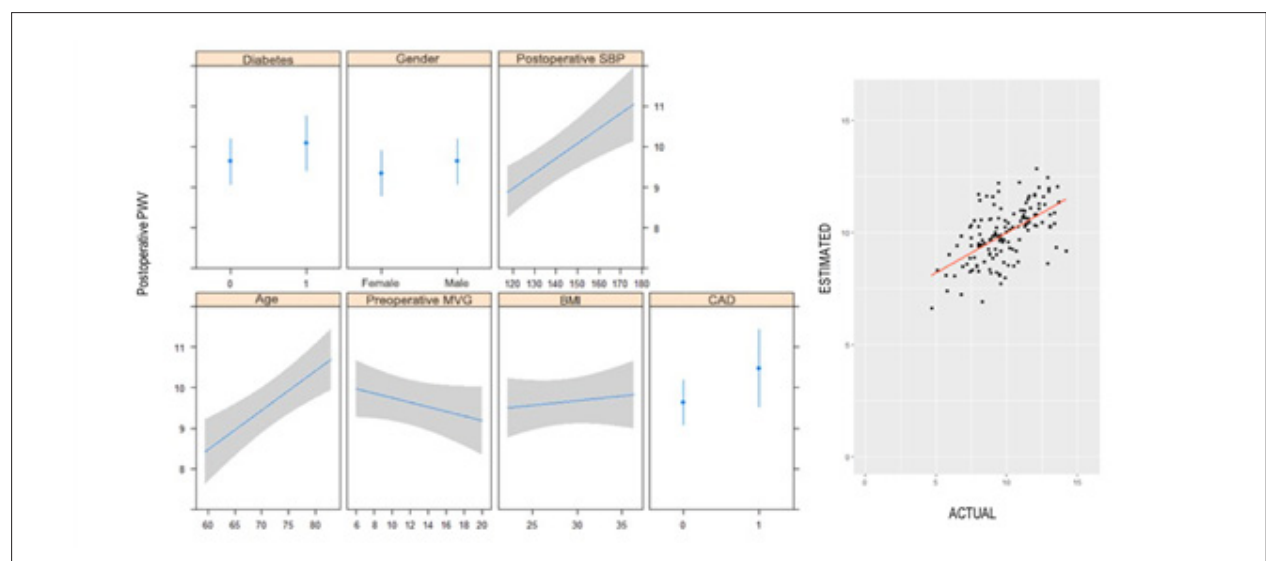


Figure 4 – Multivariable linear regression model of postoperative PWV and estimated versus actual values. BMI: body mass index; CAD: coronary artery disease; MVG: mean valve gradient; SBP: systolic blood pressure.

Previous studies have shown vascular dysfunction in obese patients,^{31,32} but in our study, body mass index (BMI) was not considered an independent predictor factor for higher pre- and postoperative PWV.

The estimated impact of AS in PWV will still be open to debate, as our study had several limitations: 1) single-center study; 2) retrospective nature, which leads to some missing data (9% missing in the multivariable analysis performed), postoperative PWV measurements not systematically programmed and performed at the same time after surgery (2 patients whose surgeries were postponed to 12 and 65 days after preoperative PWV measurement), and absence of long-term measurement; 3) the sample selection was neither randomized nor consecutive, and its relatively small size limits the external generalization of results; 4) PWV measurements also have limitations such as high variability according to patient status; for example, blood pressure could be not

controlled in the preoperative measure (all patients fasting and with discontinuation of pharmacological therapy) compared to postoperative measure (all patients without fasting and some of them with pharmacologically-controlled blood pressure).

Conclusion

Although some studies suggest that aortic stiffness is increased in AS due to a concomitant atherosclerotic component, our findings suggest that AS may blunt the real arterial stiffness of the aortic wall, as the severity of AS is inversely related to PWV, while a small increase in PWV was observed after AVR surgery and ventricular-aortic pressure gradient relief. As expected, age and SBP were independent determinants of higher PWV in patients with severe AS and remained the same after surgery. Further studies will be needed to provide better insight into the natural history of AS and its relation to vascular function.

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Author Contributions

Conception and design of the research: Raimundo R, Saraiva F, Moreira R, Moreira S, Ferreira AF, Cerqueira RJ, Amorim MJ, Lourenço AP, Leite-Moreira A; Acquisition of data: Raimundo R, Saraiva F, Moreira R, Moreira S, Ferreira AF;

Analysis and interpretation of the data and Statistical analysis: Raimundo R, Saraiva F, Moreira R, Barros AS, Lourenço AP, Leite-Moreira A; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Raimundo R, Saraiva F, Moreira R, Moreira S, Ferreira AF, Cerqueira RJ, Amorim MJ, Pinho P, Barros AS, Lourenço AP, Leite-Moreira A.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Arterial Stiffness in Aortic Stenosis

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Short Editorial related to the article: Arterial Stiffness Changes in Severe Aortic Stenosis Patients Submitted to Valve Replacement Surgery

The paper “Arterial Stiffness Changes in Severe Aortic Stenosis Patients Submitted to Valve Replacement Surgery” has important information on the behavior of arterial stiffness before and after aortic valve replacement.¹

They studied 150 patients with severe aortic stenosis submitted to aortic valve replacement with bioprosthesis. They used a noninvasive method, carotid-femoral pressure wave velocity (PWV) measured through Complior Analyse, to study arterial stiffness. Other methods could have been used, such as invasive pressure catheter measurements, MRI and peripheral cuff sensors, but PWV is the gold standard.²

Aging, hypertension and atherosclerotic disease contributes to the increase in vascular stiffness as measured by PWV and are confounding factors. Their patients’ mean age was 72 ± 8 years, hypertension was present in 83%, dyslipidemia in 76%, diabetes in 35% and 24% had a history of smoking.

There was an inverse association between arterial stiffness and the left ventricle-aortic gradient in the preoperative patients. After aortic valve replacement, there was a significant increase in arterial stiffness measured by PWV, being 9.0 ± 2.1 m/s in the preoperative and 9.9 ± 2.2 m/s (± 2.2 months after surgery) in the postoperative period. They postulated that the upstream obstruction might interfere with the measurements, masking the real effects on the aorta. Yotti et al.³ have shown that after relieving the obstruction there is an increase in the vascular load, arterial pressure and vascular impedance, inducing a vascular behavior that shows stiffness.

The study has some limitations: single center, retrospective, variability regarding the time of postoperative measurements,

lack of randomization, small sample size and variability of data according to patient status.

Singh et al.,⁴ studying 174 patients using MRI have demonstrated that in patients with aortic stenosis, those with bicuspid aortic valve (BAV) have lower aortic stiffness when compared to those with tricuspid valves (TAV), despite increased aortic dimensions, but the authors found no such difference, although there was no mention regarding the number of BAV patients in the sample.

The impact of studying arterial stiffness deserves special attention, as modifications in the arterial wall will lead to an increase in the arterial stiffness, which may be responsible for accelerated vascular aging and arterial hypertension; moreover, arterial stiffness have been incorporated into the risk stratification of subclinical target organ lesions.⁵ Vlachopoulos et al.⁶ have shown that an increase of the PWV of 1 m/s was associated with an increase in cardiovascular and all-cause mortality. Saeed et al.,⁷ studying 103 asymptomatic patients with moderate to severe aortic stenosis, have shown that patients with elevated PWV were associated with a higher risk of cardiovascular disease and death.

Another problem that is sometimes associated with aortic stenosis is the need to replace the ascending aorta with a graft, or implant an endograft in the ascending, descending aorta or aortic arch. de Beaufort et al, in an experimental study with 20 patients with porcine aortas, demonstrated that PWV was significantly increased after stent graft deployment.⁸

As the authors¹ state in their conclusion, the study of arterial stiffness may give better insights into the natural history of aortic stenosis and its association with the vascular function.

Keywords

Aortic Valve/surgery; Aortic Valve Stenosis/surgery; Aortic Valve Replacement/methods; Pulse Wave Analysis; Blood Pressure.

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Kawasaki Disease: Predictors of Resistance to Intravenous Immunoglobulin and Cardiac Complications

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Abstract

Background: Kawasaki disease (KD) is the leading cause of acquired cardiac disease in children, in developed countries.

Objectives: To identify predictive factors for resistance to intravenous immunoglobulin (IVIG), calculate the effectiveness of Japanese predictive models and characterize cardiac complications.

Methods: Retrospective analysis of KD cases admitted in a Portuguese paediatric hospital between January 2006 and July 2018. ROC curves were used to determine predictive factors for resistance and the multivariate logistic regression analysis was used to develop the predictive model. A significance level of 5% was used.

Results: 48 patients with a median age of 36 months were included. The IVIG resistance was 21%. Echocardiographic anomalies were noted in 46%, with coronary involvement in 25% of the sample population. As predictive variable of resistance, the C-reactive protein (CRP) presented an AUC ROC = 0.789, optimal cut-off value 15.1 mg/dL, sensitivity (Sn) 77.8% and specificity (Sp) 78.9%. The erythrocyte sedimentation rate (ESR) presented an AUC ROC = 0.781, optimal cut-off value 90.5 mm/h, Sn 66.7% and Sp 85.7%. The model with the two variables showed $p = 0.042$ and AUC ROC = 0.790. Predictive strength of Japanese models were: Kobayashi (Sn 63.6%, Sp 77.3%), Egami (Sn 66.7%, Sp 73.1%), Sano (Sn 28.6%, Sp 94.1%).

Conclusion: CRP and ESR are independent variables that were related to IVIG resistance, with optimal cut-off points of 15.1 mg/dL and 90.5 mm/h, respectively. About half of the patients had some form of cardiac involvement. The Japanese models appeared to be inadequate in our population. (Arq Bras Cardiol. 2021; 116(3):485-491)

Keywords: Kawasaki Disease/complications; Mucocutaneous Lymph Node Syndrome/complications; Drug Resistance; Coronary Artery Disease; Immunoglobulin; Child.

Introduction

Kawasaki disease (KD) is an acute self-limiting vasculitis, which affects medium-sized vessels and is the leading cause of acquired cardiac disease in pediatric age groups.¹

Its etiology remains uncertain, but several factors have been associated to it, namely genetic, environmental, and inflammatory ones.² Although with a worldwide distribution, its highest prevalence is in Japan, where the incidence is on the rise.³ In Portugal, an epidemiological study carried out in 2017 showed a mean annual incidence of 6.5 per 100,000 children under 5 years of age.⁴

Based on the 2004 American Pediatric Academy criteria,⁵ classic KD is considered if fever persists for five days or more and if at least four of five additional clinical criteria are observed:

nonexudative bilateral conjunctivitis, alterations of the lips and oral cavity, erythematous rash, changes in the extremities, and cervical lymphadenopathy. If fever lasts for five or more days and only two or three additional criteria are present, it is considered atypical KD, if supported by laboratory and echocardiographic data.²

If not treated within an established period, KD can be complicated by coronary artery aneurysms (CAA) in up to 25% of cases.² Although coronary artery involvement is the most feared consequence of the disease, other cardiac complications are possible.^{2,6-8} Treatment with intravenous immunoglobulin (IVIG) in the acute phase administered in the first 10 days of illness reduces the incidence of CAA to 4%.² IVIG resistance occurs in 10-20% of cases, increasing the likelihood of coronary involvement.² There are different possible approaches in case of IVIG resistance, such as a second dose of IVIG, corticosteroids and/or monoclonal antibodies.⁹ No benefit has been described when corticosteroids are used in addition to IVIG in the first instance and this therapeutics is currently reserved for refractory cases.¹⁰ In order to identify the cases that could potentially be resistant to treatment with IVIG, and benefit from adjuvant therapies in the initial phase, models based on a scoring system have been developed. Three have been validated in the Japanese population, namely the Kobayashi,¹¹ Egami,¹² and Sano scoring

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systems.¹³ However, several studies have shown that these models are poor predictors in many western populations.^{10,14,15}

The aim of this study was to identify clinical and laboratory predictive factors regarding resistance to IVIG and coronary artery involvement, and to develop a more suitable predictor model of resistance in this population. Secondary objectives regard characterizing the KD cases admitted to a central pediatric hospital over a period of 13 years, to verify the effectiveness of the Japanese scoring systems in our population sample and to analyze the non-coronary cardiac complications of KD.

Methods

Sample

Retrospective analysis of KD cases admitted to the Hospital Pediátrico – Centro Hospitalar e Universitário de Coimbra (HP-CHUC) diagnosed from 01/01/2006 to 06/30/2018. All patients between 30 days and <18 years with KD and treated with IVIG at diagnosis at HP-CHUC were included in the study. All the patients transferred from outlying centers with a diagnosis of KD and managed at these institutions were excluded.

The diagnosis of typical and atypical KD was based on the American Academy of Pediatrics criteria. We considered day one of fever on the day the fever started, defined as axillar temperature $\geq 38^{\circ}\text{C}$.

Resistance to IVIG was considered if the fever persisted 36 hours after its administration. All patients who received corticosteroids simultaneously with the first dose of IVIG were excluded from the resistance quantification.

Dallaire z scores were used to classify the coronary artery morphology defining: coronary artery ectasia if z score between 2 and 2.4, small aneurysm if z score between 2.5 and 4.9, medium aneurysm if z score between 5 and 9.9 and absolute dimension < 8 mm, and giant aneurysm if z score ≥ 10 or absolute dimension ≥ 8 mm. If unable to calculate the z score, the absolute dimensions were used, being small aneurysm if ≥ 2.5 mm and < 4mm, medium aneurysm if ≥ 4 mm and < 8 mm and giant aneurysm if ≥ 8 mm.

Regarding other cardiac complications, the coronary artery hyperchogenicity and lack of tapering on echocardiography were not considered as echocardiographic diagnostic criteria.

To calculate the effectiveness of the Japanese models, all patients who did not have the necessary data to be considered as high or low risk of IVIG resistance were excluded. Scoring and categorization in high or low risk patients were performed as shown in Table 1.

Statistical Analysis

The SPSS® (IBM®, SPSS® Statistics Inc., Chicago) program version 25.0 was used to perform the statistical analysis. The Shapiro-Wilk test was used to test the normality of the variables. The continuous variables with normal distribution were described using mean and standard deviation (SD) and continuous variables without normal distribution were described using median and interquartile range (IQR). We used the Fisher's exact test to compare categorical variables, the Student's t-test to compare

Table 1 – Scoring system of the Japanese models

Model	Score	High risk
Kobayashi		
AST > 100 U/L	2	≥ 4 points
Na ≤ 133 mmol/L	2	
IVIG with fever ≤ 4 days	2	
Neutrophils/Leucocytes ≥ 80%	2	
CRP ≥ 10 mg/dL	1	
Age ≤ 1 year old	1	
Platelets ≤ 300,000/μL	1	
Egami		
ALT ≥ 80 U/L	2	≥ 3 points
IVIG with fever ≤ 4 days	1	
CRP ≥ 8 mg/dL	1	
Age ≤ 6 months	1	
Platelets ≤ 300,000/μL	1	
Sano		
AST > 200 U/L	1	≥ 2 points
Total bilirubin ≥ 0.9 mg/dL	1	
CRP ≥ 7 mg/dL	1	

AST: aspartate transaminase; U: international unity; L: liter; Na: serum sodium; mmol: millimole; IVIG: intravenous immunoglobulin; CRP: C-reactive protein; mg: milligram; dL: deciliter; μL : microliter; ALT: alanine transaminase.

parametric variables and the Mann-Whitney test to compare the non-parametric ones. The Receiver Operating Characteristic (ROC) curves were used to evaluate the individual discriminative capacity of each variable and to identify the optimal cutoff points to predict resistance to IVIG. The variables were considered as good predictors if the area under the curve (AUC) > 0.75. Multivariate logistic regression analysis was used to develop the predictive resistance model. A significance level of 5% was used.

Results

Forty-eight patients met the KD criteria, of whom 32 (66.7%) were male. The median age was 36 months (IQR 16.75-89.25), 62.5% of patients were less than five years old and 10.4% over nine years old. On the day of admission, all the patients presented with fever, with a median duration of five days (IQR 4-8), minimum of one day and maximum of 14 days. Among the five main clinical criteria, nonexudative bilateral conjunctivitis was observed in 94% of cases, alterations of the lips and oral cavity in 90%, erythematous rash in 84%, changes in extremities in 75%, and cervical lymphadenopathy in 69%. The most common findings among oral alterations were cheilitis (67%) and lip erythema (67%), followed by erythema of the oropharynx (50%) and the strawberry tongue (48%). The most prevalent changes in the extremities were erythema (52%), followed by swelling (31%) and peeling (25%). Inflammatory signs at the Bacillus Calmette-Guérin (BCG) vaccination site were observed in 23% of patients. Atypical KD was diagnosed in 17% of the cases. The median duration of hospital stay was two days (IQR 1-6.75).

During the acute phase, IVIG 2g/kg was administered to all patients. The median day of illness of the administration was 6.5 (IQR 5-8). Simultaneously, 45-100mg/kg of acetylsalicylic acid (ASA) were administered to 47 patients in the acute phase. Five children received corticosteroids together with the first dose of IVIG. After the acute phase, all patients were medicated with ASA 3-5 mg/kg/day, three patients with clopidogrel and one with enoxaparin. Nine patients were resistant to the IVIG (21%), of which one had atypical KD ($p = 0.543$). All nine repeated IVIG administration, five of which with methylprednisolone 30 mg/kg/day.

Among the variables evaluated as predictors of IVIG resistance (Table 2), C-reactive protein (CRP) presented an AUC ROC of 0.78 (95% confidence interval (CI): 0.632 – 0.947), and the erythrocyte sedimentation rate (ESR), an AUC ROC of 0.781 (95%CI: 0.585 – 0.977). The optimal cut-off value for CRP was 15.1 mg/dL with sensitivity (Sn) of 77.8% and specificity (Sp) of 78.9% (Odds ratio (OR) = 13.125 95%CI: 2.271 – 75.858). The optimal cut-off value for ESR was 90.5 mm/h, with Sn of 66.7% and Sp of 85.7% (OR = 12.000 95%CI: 1.718 – 83.803). A logistic model was developed with these two variables, with a p-value of 0.042, AUC ROC of 0.79 (95%CI: 0.589 – 0.992), with Sn of 83.3% and Sp of 77.1%, but with a 25% variance (Nagelkerke $R^2 = 0.254$).

Coronary artery changes were found in 12 children (25%), seven with ectasia and five with CAA. The comparison between groups with and without coronary artery involvement is shown in Table 3. The duration of fever and the use of corticosteroids were the only significant differences between these two groups. Patients with coronary artery involvement had longer duration of fever ($p = 0.038$) and greater need for corticotherapy ($p = 0.009$). Four patients had CAA when methylprednisolone was started. Among the five patients with CAA, three met the criteria for small aneurysms, one for

medium aneurysms and one for giant ones. These patients are summarized in Table 4.

In the acute phase, in addition to coronary involvement, 10 patients presented with pericardial effusion, three with mild mitral valve regurgitation, two with left ventricular systolic dysfunction, one with cardiogenic shock and one with variable first degree atrioventricular (AV) block. After the acute phase, the patient with the AV block developed left ventricle (LV) dilation and another patient developed LV hypertrophy.

Table 5 summarizes Sn, Sp, and the positive (PPV) and negative predictive values (NPV) for the Japanese models in our sample.

Discussion

Despite the lower incidence compared to Japan, KD is a vasculitis that is still an important cause of pediatric disease in our population. Early diagnosis and management are two important factors that appear to reduce cardiac involvement.

Our study revealed an incidence of IVIG resistance similar to the 10 to 20% described in the literature.² Over the years, efforts have been made to find clinical and laboratory factors that can predict this resistance in order to introduce adjuvant therapies at an early stage of the disease. There are several parameters in the literature that have been studied for this purpose, such as age, serum albumin, transaminases, total bilirubin, neutrophils count, platelet count, CRP, ESR, among others.^{14,16–20} In our study, CRP and ESR presented a statically significant predictive capacity in relation to IVIG resistance. For CRP, the optimal cut-off point was 15.1 mg/dL (Sn 77.8%, Sp 78.9%, OR 13.125). Patients with CRP values above 15.1 mg/dL are about 13 times more likely to be resistant to IVIG than those with lower values. Concerning ESR, the optimal cut-off point was 90.5 mm/h (Sn 66.7%, Sp 85.7%, OR 12.000). Patients with ESR greater than 90.5 mm/h have a probability of resistance to IVIG approximately 12 times higher than those with lower values. Combining these two independent variables, a statistically significant model was obtained ($p = 0.042$), whose cut-off point has Sn of 83.3% and Sp of 77.1%. Despite these encouraging results, the variance explained by the model is only 25% (Nagelkerke $R^2 = 0.254$). Thus, although statistically significant, it cannot be validated, which is largely due to the small sample size. Nevertheless, based on these trends, the base-line values for CRP and ESR should be known prior to IVIG administration. The resistance predictor capacity highlights the role of inflammation in this disease, a possible underlying trigger in KD vasculitis.²¹

The etiology of KD remains uncertain, however, predisposing factors have been put forward. One, is the immaturity of the immune system, a theory that is supported by the fact that KD predominantly affects children under the age of five. In our study, 62.5% of the patients belonged to this age group, which, although corresponding to the majority of the sample, is below the 80% described in the literature.¹ A possible explanation for this result is genetic contribution, since the incidences described in the literature are from studies with a wide range of ethnicities, including Asian children.

Coronary artery involvement occurred in 12 (25%) children, seven with ectasia and five with CAA. Therefore, the incidence

Table 2 – Receiver operating characteristic analysis of several variables to predict resistance to intravenous hemoglobin

Characteristic	AUC [95%CI]
Age	0.542 [0.377; 0.708]
IVIG administration day	0.595 [0.403; 0.787]
Hemoglobin	0.611 [0.416; 0.806]
Leucocytes	0.525 [0.331; 0.719]
Neutrophils	0.637 [0.447; 0.828]
Platelets	0.513 [0.295; 0.732]
ESR	0.781 [0.585; 0.977]
CRP	0.789 [0.632; 0.947]
Na	0.715 [0.475; 0.955]
AST	0.648 [0.434; 0.862]
ALT	0.693 [0.486; 0.901]
Total bilirubin	0.500 [0.139; 0.861]
Albumin	0.693 [0.459; 0.928]

AUC: area under the curve; CI: confidence interval; IVIG: intravenous immunoglobulin; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; Na: serum sodium; AST: aspartate transaminase; ALT: alanine transaminase.

Table 3 – Characteristics of groups with and without coronary artery involvement

Characteristics	Without coronary involvement (n =36)	Coronary involvement (n= 12)	p - value
Corticoid (n=10) n	4	6	0.009
Resistance to IVIG (n=9) n	5	4	0.173
Age (months) Mean ± sd	59.7 ± 57	47.5 ± 30.1	0.35
Fever duration (days) Mean ± sd	7.4 ± 2.8	9.4 ± 3	0.038
IVIG administration day Mean ± sd	6.5 ± 2.9	7.6 ± 3.5	0.283
Atypical KD n	6	2	0.686
Haemoglobin (g/dL) Mean ± sd	11.5 ± 1.3	11.2 ± 1.3	0.359
Leucocytes (/μL) Mean ± sd	14,174 ± 6,010	15,216 ± 6,918	0.619
Neutrophils (/μL) Mean ± sd	9,515 ± 4,770	10,994 ± 5,629	0.378
Platelets (/μL) Mean ± sd	328,389 ± 127,125	362,667 ± 282,652	0.691
CRP (mg/dL) Mean ± sd	10.4 ± 8.8	19.6 ± 25	0.243
ESR (mm/h) Mean ± sd	71.6 ± 19	76.7 ± 33.4	0.672
Na (mmol/L) Mean ± sd	137 ± 4	137 ± 5	0.869
AST (U/L) Mean ± sd	64 ± 53	101 ± 91	0.222
ALT (U/L) Mean ± sd	99 ± 116	113 ± 86	0.712
Total bilirubin (mg/dL) Mean ± sd	1.9 ± 2	2.8 ± 3	0.538
Albumin (g/L) Mean ± sd	35.6 ± 4.3	34.9 ± 7.2	0.77

n: absolute value; IVIG: intravenous immunoglobulin; sd: standard deviation; KD: Kawasaki disease; g: gram; dL: deciliter; μL: microliter; CRP: C-reactive protein; mg: milligram; ESR: erythrocyte sedimentation rate; h: hour; Na: serum sodium; mmol: millimole; L: litre; AST: aspartate transaminase; U: international unit; ALT: alanine transaminase.

of CAA was 10%, which is higher than the 4% reported in the literature. Comparing the groups with and without coronary artery involvement, a statistically significant difference was found regarding the duration of fever ($p = 0.038$). This result highlights the deleterious effects of persistent fever and the need for IVIG administration, preferably up to the tenth day of the disease, in order to avoid cardiac sequelae.⁹ The use of corticosteroids in KD is still a topic of debate and controversy. The most consensual is the use intravenous methylprednisolone (MPDN) at a dose of 15 to 30 mg/kg/day, for three days.⁹ In patients with refractory KD, MPDN suppresses the inflammatory cytokine levels more quickly than a second dose of IVIG,⁹ although it is not recommended as a first-line treatment. Sleeper et al.¹⁰ evaluated the impact of corticosteroids at different times of the disease and showed

that, with regards to the development of CAA, the only statistically significant difference was in those refractory to the first dose of IVIG which combined corticosteroids with the second dose of IVIG.

The cardiac complications and echocardiographic findings, others than coronary artery involvement were also evaluated. Three cases of left ventricular systolic dysfunction were identified, one of which with cardiogenic shock, a complication also described in the literature.^{2,7} In the acute phase, ten patients presented with pericardial effusion without hemodynamic compromise, three patients with mild mitral valve regurgitation and one with first degree AV block. Chbeir et al.²² found a relation between resistance to IVIG, CAA, and initial cardiac echocardiographic findings such as pericardial effusion, coronary hyperechogenicity, and

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Table 4 – Characteristics of patients with coronary artery aneurysms

Characteristics	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (months)	12	60	108	63	4
Male	Yes	Yes	Yes	Yes	Yes
Fever duration (days)	7	6	8	9	14
Classic KD	Yes	Yes	Yes	Yes	No
Day of fever in IVIG 1 st dose	7	6	4	6	14
Resistance to IVIG	No	No	Yes	Yes	NA
Day of fever in IVIG 2 nd dose	NA	NA	6	8	NA
MPDN (30mg/Kg/day)	No	No	Yes	Yes	Yes
With IVIG 1 st dose	NA	NA	No	No	Yes
With IVIG 2 nd dose	NA	NA	Yes	Yes	No
CAA classification	Small	Small	Small	Medium	Giant
Maximum z score	NA	4.46	3.56	6.94	13.81
Arteries involved	RCA; CT	RCA; LCA	LCA	RCA; LCA	RCA; LAD; LCX

KD: Kawasaki disease; IVIG: intravenous immunoglobulin; MPDN: methylprednisolone; mg: milligram; Kg: kilogram; CAA: coronary artery aneurysms; RCA: right coronary artery; CT: common trunk; LCA: left coronary artery; LAD: left anterior descending artery; NA: not applicable; LCX: left circumflex artery.

Table 5 – Statistical values of the Japanese models in our study

Model	n	Sn (%)	Sp (%)	PPV (%)	NPV (%)
Kobayashi	34	63.6	77.3	53.8	81
Egami	39	66.7	73.1	50	82.6
Sano	25	28.6	94.1	66.7	77.3

n: absolute value; Sn: sensitivity; Sp: Specificity; PPV: positive predictive value; NPV: negative predictive value.

coronary ectasia. The coronary hyperechogenicity and the lack of tapering on echocardiography were not considered as relevant factors, since they are subjective findings, poorly reproducible and can be found both in febrile illnesses and in healthy children.²³ During the chronic phase, one patient remained with conduction system impairment and developed LV dilation, and another patient developed LV hypertrophy. The long-term cardiac repercussions in KD remain unclear. Friedman et al.⁶ reported an increase in the occurrence of long-term adverse cardiac effects, leading to primary angioplasty, coronary bypass surgery, heart transplantation, and death, in patients who developed CAA with higher z scores and who were initially resistant to IVIG. A study by Holve et al.⁸ revealed a low incidence of adverse cardiac effects in subjects up to 21 years of age, but a greater likelihood of developing high blood pressure from the age of 15.

Japanese predictive models presented poor clinical utility in this study (Table 4). The model with the highest specificity was Sano's, although with very low sensitivity and with only a small number of cases included. Egami's model was the most sensitive, however, not powerful enough to be validated. The genetic component may be the explanation for these differences. In fact, the results presented here are similar to those of other studies carried out outside Japan, in which none

were able to validate the models in their samples.^{10,14-17,20} It is still important to note the differences in the study design in relation to the Japanese models, namely that they were applied only to patients with classical KD. Another Japanese study failed to validate the models in a sample exclusively composed of atypical KD cases.²⁴ The Kobayashi model was validated for the Japanese population with Sn of 86% and Sp of 67%.¹¹ Contrary to the present study, IVIG was administered at a dose of 1 g/kg on two consecutive days and resistance was considered if fever persisted 24 hours after the beginning of the treatment, or in case of recurrence after a period without fever. The Egami model was validated with Sn of 78% and Sp of 76%, however, resistance was considered if the CRP value did not decrease by more than 50% and fever persisted for longer than 48 hours after IVIG administration.¹² Loomba et al.²⁵ were not able to validate the Egami model even when applying it separately to classical and atypical KD, and by ethnicity. The Sano model, validated with Sn of 77% and Sp of 86%, was the only one of the three to adjust the size of the CAA to the body surface.¹³ However, it also used IVIG at a dose of 1 g/kg on two consecutive days and defined resistance if fever persisted 24 hours after the end of therapy.

The main limitations of this analysis are related to its retrospective methodology and sample size.

Conclusions

CRP and ESR are independent variables that showed a predictive trend regarding resistance to IVIG, with optimal cut-off values of 15.1 mg/dL and 90.5 mm/h, respectively. However, there is a need for a multicenter study with a sample of adequate dimensions to validate a model based on these two analytical parameters. Cardiac complications are not limited to coronary arteries, and the study and follow-up of these patients should be more widespread. The validated models for the Japanese population have very limited utility in our population, further reinforcing the need and importance of new approaches.

Author Contributions

Conception and design of the research: Faim D, Henriques C, Brett A, Francisco A, Rodrigues F, Pires A; Data acquisition: Faim D, Henriques C; Analysis and interpretation of the data: Faim D, Brett A, Francisco A; Statistical analysis and Writing of the manuscript: Faim D; Critical revision of the manuscript for

intellectual content: Faim D, Brett A, Francisco A, Rodrigues F, Pires A.

Potential Conflict of Interest

The authors report no conflict of interest concerning the materials and methods used in this study or the findings specified in this paper.

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Original Article

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Kawasaki Disease: Predictors of Intravenous Immunoglobulin Resistance and Cardiac Complications: New Perspectives?

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Short editorial related to the article: Kawasaki Disease: Predictors of Resistance to Intravenous Immunoglobulin and Cardiac Complications

Kawasaki disease (KD) is an acute inflammatory disease of unknown origin and associated with vasculitis. It affects medium-sized vessels. Coronary artery abnormalities (CAA) — aneurysms or dilations — are the main complications of KD, and are currently the most common cause of heart disease acquired in children in developed countries. In the acute phase, the initial standard treatment recommended is intravenous immunoglobulin (IVIG) and aspirin, to reduce the risk of damage to the coronary arteries.¹ However, 10 to 20% of children with KD do not respond to the initial standard treatment, with recurrent fever within 36 to 48 hours after IVIG infusion. Studies show that the likelihood of KD patients resistant to IVIG to have coronary artery lesions is nine times greater than those sensitive to IVIG. This suggests that there is a critical window to block the inflammatory process and prevent CAA in the long term.²

The study by Faim et al.³ aimed to identify predictive factors for resistance to intravenous immunoglobulin (IVIG), calculate the effectiveness of Japanese predictive models and characterize the cardiac complications of patients followed up at a single institution.³

Of the 48 KD patients included in the study between 2006 and 2018, 17% were diagnosed with atypical KD. All had fever on the day of admission, with a median of five days, and all were treated in the acute phase with IVIG and aspirin, with a median of 6.5 days. Resistance to IVIG has been described in 9 cases (21%), one of which of atypical KD. These findings are consistent with literature data.⁴

For the early identification of patients resistant to IVIG and to enable the early introduction of other treatment strategies, studies have been carried out trying to establish clinical and laboratory criteria that predict IVIG resistance, such as age, albumin dosage, transaminases, hemoglobin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), platelets, bilirubins, sodium, and others.⁴ In the study, the authors constructed ROC curves to find predictive factors for resistance and developed a predictive model using multivariate logistic regression. Analyzing the predictive variables of resistance,

CRP presented an AUC ROC = 0.789, cut-off point = 15.1 mg/dL, sensitivity (S) = 77.8% and specificity (E) = 78.9%. The ESR presented an AUC ROC = 0.781, a cut-off point = 90.5 mm/h, S = 66.7% and E = 85.7%. The predictive model with the two variables showed $p = 0.042$ and AUC ROC = 0.790.

Literature data are controversial regarding the use of ESR as a predictor of IVIG resistance. In a meta-analysis, Baeck et al.,⁵ aiming to identify laboratory factors predictive of IVIG resistance, included twelve studies published between 2006 and 2014, analyzing 2,745 patients. Of these, seven studies calculated the ESR effect size as a predictive factor of IVIG-resistant KD. Heterogeneity between these studies was low ($Q(6) = 11.001$, $P > 0.001$, $I^2 = 45.459$) and the meta-analysis found that the effect size was small for ESR (random effects, 0.150).⁵

In a meta-analysis performed by Xuan Li et al., analyzing 28 studies involving 26,260 patients, about 4,442 patients were diagnosed with IVIG-resistant KD and 21,818 patients were diagnosed with IVIG-sensitive KD. The meta-analysis showed that ESR in the IVIG-resistant group was significantly higher than in the IVIG-sensitive group. However, the strong association between ESR and KD was demonstrated only in two studies in a Chinese population. The same findings were not shown in Koreans, Japanese and non-Asians. The other studies had a weak association between ESR and IVIG resistance.⁶

The guideline on Kawasaki disease published in 2017 by the American Heart Association,¹ points out that the ESR increases with IVIG and should not be used to assess therapeutic response, and persistently high ESR should not be interpreted as a sign of resistance to IVIG therapy (Class III, LE: C).

Therefore, we must carefully analyze the use of ESR as an independent risk predictor for IVIG resistance in the non-Asian population.

The three models of risk scores developed, namely Kobayashi et al.,⁷ Sano et al.⁸ and Egami et al.,⁹ validated for the Japanese population,⁷⁻⁹ do not work properly in western, ethnically mixed and Chinese populations.¹⁰⁻¹⁴ A similar situation was observed by Faim et al.,³ where the respective models validated in Japan did not perform well either.³

It is worth noting that in the study by Faim et al. about 25% of the patients had coronary involvement, 40% of them had aneurysm formation, in addition to other cardiovascular complications. CAA and other cardiovascular complications in the acute phase, including myocarditis, cardiogenic shock and pericardial effusion, are described in the literature.^{1,2,4}

Regardless of the size of the sample analyzed and its retrospective nature, the study findings are comparable to literature data, demonstrating the complexity of the disease and the need for further research aiming to define the best predictive model of IVIG resistance and potentially reduce the main KD complication.

Keywords

Mucocutaneous Lymph Node Syndrome/trends; Kawasaki Disease; Coronary Artery/abnormalities; Vasculitis; Children; Immunoglobulins, Intravenous; Drug Resistance.

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GDF-15 as a Biomarker in Cardiovascular Disease

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Abstract

In the last years, several diagnostic and prognostic biomarkers have been studied in cardiovascular disease. Growth differentiation factor-15 (GDF-15), a cytokine belonging to the transforming growth factor- (TGF-) family, is highly up-regulated in stress and inflammatory conditions and has been correlated to myocardial injury and pressure cardiac overload in animal models. This new biomarker has been positively correlated with increased risk of cardiovascular events in population studies and shown an independent predictor of mortality in patients with coronary artery disease and heart failure. This review aimed to summarize the current evidence on the diagnostic and prognostic value of GDF-15 in different settings in cardiology.

Introduction

The growth differentiation factor-15 (GDF-15) is a cytokine belonging to the transforming growth factor beta (TGF- β) family, with low concentrations in tissue and plasma, except for the placenta and prostate. GDF-15, discovered more than 20 years ago, was formerly named the macrophage inhibitory cytokine-1 (MIC-1) due to its possible role as an antagonist of macrophage activation by inflammatory cytokines (interleukins and tumor necrosis factor) in experimental studies. The role of this cytokine in human body has not been elucidated yet and seems to vary with tissue types. The expression of this marker is upregulated by stress and tissue damage, and is associated with inflammatory conditions of different organs, including the myocardium.¹

In animal models, the GDF-15 was initially reported as a cardioprotective protein, preventing cell death, and cardiac dilatation and hypertrophy. An increased expression of this marker was seen in response to damaging stimuli, such as pressure overload and tissue ischemia.^{2,3} The activation of nitric oxide synthase (NOS-2) enzyme in stressful situations is involved in the up-regulation of GDF-15 via intracellular

signaling pathways, depending on nitric oxide.³ In genetically modified rats deficient in GDF-15, greater infarction areas with myocyte apoptosis were detected in induced myocardial infarction, suggesting a protective role of GDF-15 against myocardial injury.³ Figure 3 presents the main factors that influence the GDF-15 expression.

Another experimental study correlated the increased levels of GDF-15 in cardiomyocytes of rats with reduced activation of growth hormone (GH), suggesting the involvement of this marker in GH signaling pathway. After this finding, the same authors conducted a study on children with congenital heart disease, and found significantly higher levels of GDF-15 in plasma of children with concomitant heart disease and failure to thrive compared with healthy controls and children with heart disease and normal growth.⁴

Since then, the GDF-15 has been investigated in several clinical conditions, and associated with a greater risk for cardiovascular events in most of the studies.⁵⁻⁹ Today, the kits for determination of serum GDF-15 levels can be found commercially available in Europe, while in other regions, they are used for research and experimental purposes only.¹⁰ The measurement is made by immunoassays, by immunoradiometric assay (IRMA) that determines the amount of the radiolabeled antigen-antibody complex, by enzymes (ELISA) or by luminescence (chemiluminescence). The detection range varies from 400 to 20000 ng/L, with good precision and reproducibility (within-and between-assay imprecision lower than 10%). The most used test today is the ELISA due to its lower cost and higher accessibility.^{11,12}

The aim of this article is to review the role of GDF-15 in different cardiac diseases and evaluate the possibility of incorporating it as a biomarker in the diagnosis and risk stratification of common heart diseases.

Cardiovascular Risk in Healthy Individuals

The first human study to correlate GDF-15 with cardiovascular disease was published in 2002 and included 27,628 healthy women, followed-up for four years. The results indicated a 2.7-fold increase in the risk of developing cardiovascular events in women with GDF-15 concentrations above 856 ng/L.¹³ In a cohort of 1,391 patients with no history of heart disease, GDF-15 was an independent predictor of mortality and cardiovascular mortality, with a hazard ratio (HR) of 1.5 (95% CI 1.3-1.8), with a discriminatory power comparable to B-type natriuretic peptide (BNP) (HR 1.3; 95% CI 1.2-1.5).¹⁴

Data from the Framingham Heart study, in which 85 biomarkers were evaluated (including BNP, PCR and GDF-15) in 3,523 participants over 14 years, showed that the GDF-15 was the only marker, in a multivariate analysis, to

Keywords

Cardiovascular Diseases; Biomarkers; GDF-15 Growth Differentiation Factor 15; Cytokines; Stress; Inflammation; Prognostic.

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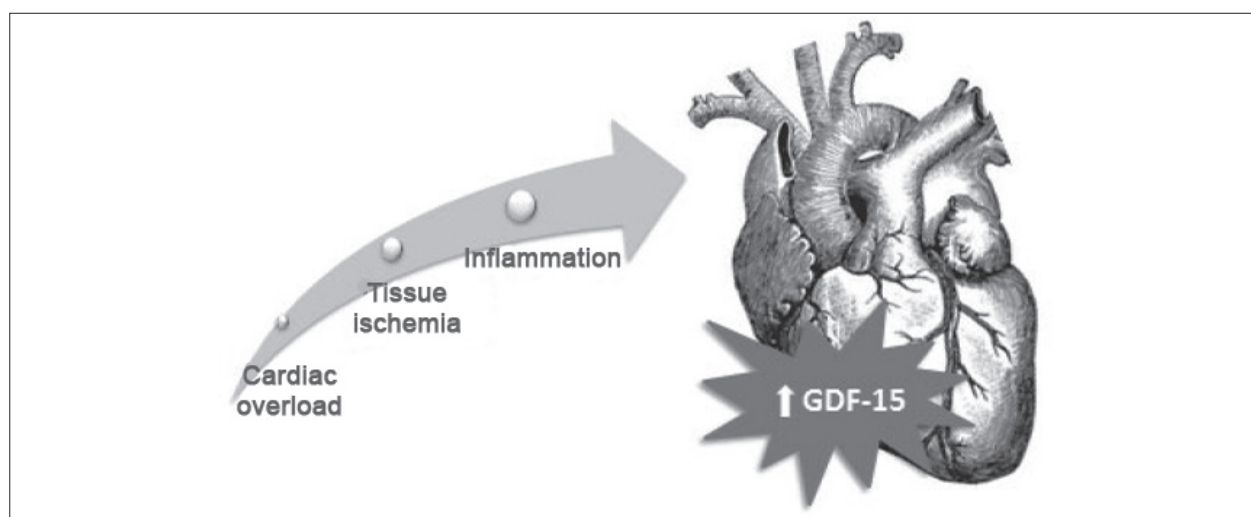


Figure 1 – Influencing factors of growth differentiation factor-15 (GDF-15) in the cardiovascular system.

show a significant association with the three outcome results: atherosclerotic events (HR 1.43; 95%CI: 1.20-1.58), heart failure (HF) (HR 2.08; 95%CI: 1.72-2.53) and mortality (HR 1.96; 95%CI: 1.76-2.17).⁸

Coronary Artery Disease (CAD)

GDF-15 was studied in patients admitted for acute coronary syndrome (ACS) and patients with stable coronary disease.

Acute Coronary Syndromes

Patients with elevated GDF-15 at admission for ACS had more events such as cardiovascular deaths, reinfarction and stroke at 12 months after discharge, indicating a prognostic value regarding the course of atherosclerotic disease.¹⁵

Another recent observational study showed the same prognostic association of GDF-15 with major cardiovascular events (overall mortality, non-fatal infarction, and hospitalization for HF). However, in a multivariate analysis adjusted for other risk factors, the GDF-15 remained significant only for mortality and development of HF.¹⁶

Still in the context of acute diseases, a clinical trial comparing invasive versus conservative strategy in non-ST-elevation acute coronary syndrome showed a significantly higher incidence of events in patients with elevated GDF-15 levels, allocated to the conservative strategy group. The authors suggested that the determination of GDF-15 should complement risk scores in the screening for patients who would benefit more of an early invasive strategy.¹⁷

In agreement with this idea, the use of the GRACE risk score, adjusted for GDF-15, combined with GDF-15 measurement at hospital admission increased the score accuracy (area under the receiver-operating characteristic curve from 0.79 to 0.85). During the six-month follow-up, 54 of the patients without events were classified into low risk according to the adjusted score.¹⁸ Tzikas et al.¹⁹ found that GDF-15 is an independent predictor of cardiovascular

events, comparable to troponin. Also, the authors observed that GDF-15 levels were strongly correlated with the severity of coronary disease assessed by the Syntax score after coronary revascularization.¹⁹

In a study on patients with ST-segment elevation myocardial infarction treated with primary percutaneous coronary intervention, the 10-year all-cause mortality rate following an acute event increased from 6% to 19% in patients GDF-15 levels above the median.²⁰ Another study evaluated GDF-15 temporal dynamics during the first 24 hours of ST-elevation myocardial infarction and showed that GDF-15 peaked at 12 h and remained elevated at 24 h. At 24 hours, higher levels of GDF-15 were correlated with higher 30-day mortality.²¹ With respect to the extension of infarction and prognosis, the higher the GDF-15 levels, the greater the risk for ventricular remodeling and dilation in 12 months.²² A prospective study analyzed 92 biomarkers in 847 patients with coronary disease followed for six years after acute infarction. GDF-15 was one of the markers with a predictive power for mortality after adjustments for clinical factors.²³

A meta-analysis of eight studies with STEMI patients, the GDF-15 was considered a strong predictor of mortality, with a relative risk (RR) of 6.08 (95%CI: 4.79-7.71; $p < 0.001$) and of non-fatal reinfarction, with a RR of 1.76 (95%CI: 1.49-2.07; $p < 0.001$).²⁴ These findings are corroborated in a more recent meta-analysis of 13 studies and 43,547 patients with ACS: RR for mortality of 6.75 (95%CI: 5.81-7.84; $p < 0.001$) and RR for non-fatal reinfarction of 1.95 (95%CI: 1.72-2.21, $p < 0.001$).²⁵

In addition, for ACS patients with indication for dual antiplatelet therapy, GDF-15 was a predictor of bleeding risk.¹⁵ In a post-hoc analysis of the PLATO trial (ticagrelor vs. clopidogrel in STEMI), patients with elevated GDF-15 (>1800 ng/L) at one month after an ACS was associated with a three-fold increased risk of bleeding, regardless of the drug used.²⁶ In this case of elevated GDF-15 levels after an acute event, a marker of bleeding risk may help in the decision to continue the dual antithrombotic therapy beyond the usual time.

Stable Coronary Disease

In chronic coronary disease, GDF-15 was measured in a cohort of 14,577 patients with stable angina and history of revascularization, multivessel disease or infarction for more than one year. During the follow-up period, GDF-15 levels above 1,827 ng/L were associated with increased risk of cardiovascular death (HR 2.63; 95%CI 1.9-3.6; $p < 0.001$), cardiac sudden death (HR 3.06; 95%CI: 1.9-4.8; $p < 0.001$) and hospitalization for HF (HR 5.8; 95%CI: 3.2-10.0; $p = 0.006$), regardless of other markers such as troponin, reactive C protein, and BNP. In this study,²⁷ no correlation was found between GDF-15 and new thrombotic event after adjustment for the other biomarkers.

Heart Failure

GDF-15 was assessed in different cohorts of patients with HF, and compared with natriuretic peptides [BNP or the N-terminal fragment of BNP precursor (NT-proBNP)]. The main difference between them was the magnitude of increase in plasma concentrations according to the type of ventricular dysfunction. NT-proBNP, a marker for hemodynamic stress on the left ventricle was more significantly increased in HF with reduced ejection fraction than in HF with preserved ejection fraction. On the other hand, GDF-15 was similarly increased in both systolic and diastolic dysfunction, suggesting that the inflammatory injury is involved in the pathophysiology of both conditions. The GDF-15 was shown to be an important predictor of adverse events and mortality, independent of ejection fraction and serum levels of NT-proBNP.²⁸⁻³³

HF with Reduced Ejection Fraction (HFrEF)

The assessment of GDF-15 in different stages of HF has revealed that the cytokine is a biomarker of disease progression, which increases exponentially with worsening of functional class and remodeling of the left ventricle. The GDF-15 levels are already elevated in the preclinical stage of HF (stage B) and its combination with NT-proBNP increased the diagnostic accuracy for HF, including at this initial stage.³⁴ In the same line of thought, another prospective study correlated GDF-15 with ventricular dysfunction progression and loss of functional capacity in patients with ejection fraction below 35%, and showed that GDF-15 levels increased with the severity of HF. This result remained significant after adjustment for other risk factors such as peak oxygen consumption (VO₂ peak), age and glomerular filtration rate.³⁵

The first large study that evaluated the prognostic value of GDF-15 in HFrEF was conducted with data from the Valsartan Heart Failure Trial (Val-HeFT) that evaluated the use of valsartan in HF patients. GDF-15 levels were evaluated in the beginning of the study ($n = 1,734$) and at 12 months of follow-up ($n = 1,517$). In the beginning of the study, 85% of patients had increased GDF-15 levels ($> 1,200$ ng/mL). In a multivariate analysis including clinical variables, BNP, troponin and C-reactive protein, elevated levels of GDF-15 were independently associated with an increase in the risk of overall mortality (HR

1.007; 95%CI: 1.001-1.014; $p = 0.02$), but not with the occurrence of the first morbid event (HR 1.003; 95%CI: 0.997-1.008; $p = 0.34$), that included death, sudden death with resuscitation, hospitalization for HF, or administration of intravenous inotropic or vasodilator drugs for more than 4 hours without hospitalization. After 12 months of follow-up, the increase in the GDF-15 values was similar for the placebo and the valsartan groups and was independently associated with overall mortality and first morbid event. This result suggests that the GDF-15 represents a pathophysiological axis that is not addressed by the therapies prescribed.⁷

More recently, the GDF-15 was studied in 1,935 patients included in the PAADIGM-HF study, which compared sacubitril/valsartan versus enalapril in patients with HFrEF. Baseline GDF-15 and the levels at one month and eight months of treatment were associated with increased risk of overall mortality and cardiovascular events (HR 1.13; 95%CI: 1.08-1.18; $p < 0.001$), combined endpoint of cardiovascular death or hospitalization for HF (HR 1.09, 95% CI 1.05-1.14, $p < 0.001$) and HF death. The increment in GDF-15 levels was not influenced by the therapies.³⁶

The role of GDF-15 was also evaluated in patients undergoing cardiac resynchronization therapy. Of 158 patients, 72% had a good response to treatment; however, patients with serum GDF-15 above 2,720 ng/L had significantly higher risk of cardiovascular mortality, and rehospitalization for HF in 2.5 years. Despite the prognostic value of GDF-15 in this population, baseline levels and changes from baseline one year after implantation failed to predict the response to the resynchronization device.³⁷

In advanced HF, five biomarkers (PCR, NT-proBNP, GDF-15, galectin-3, and troponin) were measured in patients New York Heart Association class III. Among these, GDF-15 was the marker that best predicted long-term mortality, with better predictive value as compared with NT-proBNP (area under the curve [AUC] 0.78 versus 0.63).³⁸

In patients with severe non-ischemic cardiomyopathy, GDF-15 was evaluated in myocardial tissue obtained during implantation of left ventricular assist devices or during heart transplantation, and found to be strongly correlated with the severity of myocardial fibrosis.³⁹ In this cohort, at one month after implantation of mechanical circulatory support, GDF-15 levels were significantly decreased compared with pre-implantation levels, which reinforces its association with the severity of myocardial dysfunction.³⁹

HF with Preserved Ejection Fraction (HFpEF)

Today, the diagnostic criteria for HFpEF are mainly based on HF symptoms and echocardiographic changes suggesting elevated cardiac filling pressures. However, there is still high heterogeneity of concepts and criteria adopted by the Societies and in the diagnosis in clinical practice. In HFpEF patients, elevated GDF-15 were detected, with a direct association with echocardiographic E/e ratio. The combination of NT-proBNP with elevated GDF-15 increased the diagnostic accuracy (AUC of 0.93) for HFpEF.⁴⁰ Also,

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prospective cohort studies with this population showed that the higher the GDF-15 levels, the more severe the diastolic dysfunction and NYHA functional class.^{41,42}

One diagnostic challenge is the definition of HFpEF in morbidly obese patients, due to echocardiographic limitations such as unfavorable window, multifactorial dyspnea, and reduced BNP levels. In the study by Baessler et al.,⁴³ on patients with body mass index above 30 kg/m², GDF-15 correlated with increased filling pressures at echocardiography. The inclusion of the GDF-15 in the echocardiographic criteria for diastolic dysfunction yielded better diagnostic performance in this population, compared with the combination of BNP with the same criteria (AUC 0.76 x AUC 0.56, respectively).⁴³

Acutely Decompensated HF

Serum GDF-15 concentrations of patients with acutely decompensated HF are elevated at admission (most studies have reported GDF-15 levels above 1,200 ng/L). The higher the GDF-15 concentrations, or if GDF-15 levels increased during hospitalization, the greater the risk of rehospitalizations for HF and post-discharge mortality.^{44,45}

In a study⁴⁶ with 55 patients with HFrEF, the authors conducted serial measurements of several biomarkers during hospitalization for cardiac decompensation and at 30 days of discharge, and showed that the curve of GDF-15 was similar to two other markers: suppression of tumorigenicity 2 (ST2, a biomarker belonging to the interleukin-1 receptor family) and BNP. In this study, the

rapid fall in GDF-15 levels was marked by an evident clinical improvement of patients, different to what was observed with other pro-inflammatory proteins, including C-reactive protein, TNF-alpha, IL-6, galectins and myeloperoxidase.⁴⁶

Models combining the GDF-15 with classical biomarkers such as troponin and BNP have demonstrated that the measurement of this cytokine in acute HF adds prognostic value. This data suggests that the presence of several independent pathophysiological pathways in patients hospitalized for HF, and indicates, once again, the clinical relevance of this biomarker in this scenario.^{47,48}

Figure 2 shows the main correlations of GDF-15 with clinical aspects in HF.

Sudden Death

GDF-15 was also studied in risk stratification for sudden death in patients with cardiovascular diseases. Patients with stable coronary disease and elevated GDF-15 had increased risk for sudden death (HR 3.0) (95%CI: 1.94-4.84; $p < 0.001$).²⁷

In a recent cohort study, measurements of ST2 and GDF-15 levels were determined in 52 nonischemic HF patients followed for a mean of seven years. GDF-15 was correlated with a two-fold increased risk for death for arrhythmia and sudden death with resuscitation (HR 2.2; 95%CI 1.1-4.5; $p = 0.028$) and was superior to ST2 in predicting all-cause mortality (HR 2.4; 95%CI: 1.4-4.2; $p = 0.003$ versus HR 1.6; 95%CI: 1.05-2.7; $p = 0.03$).⁴⁹

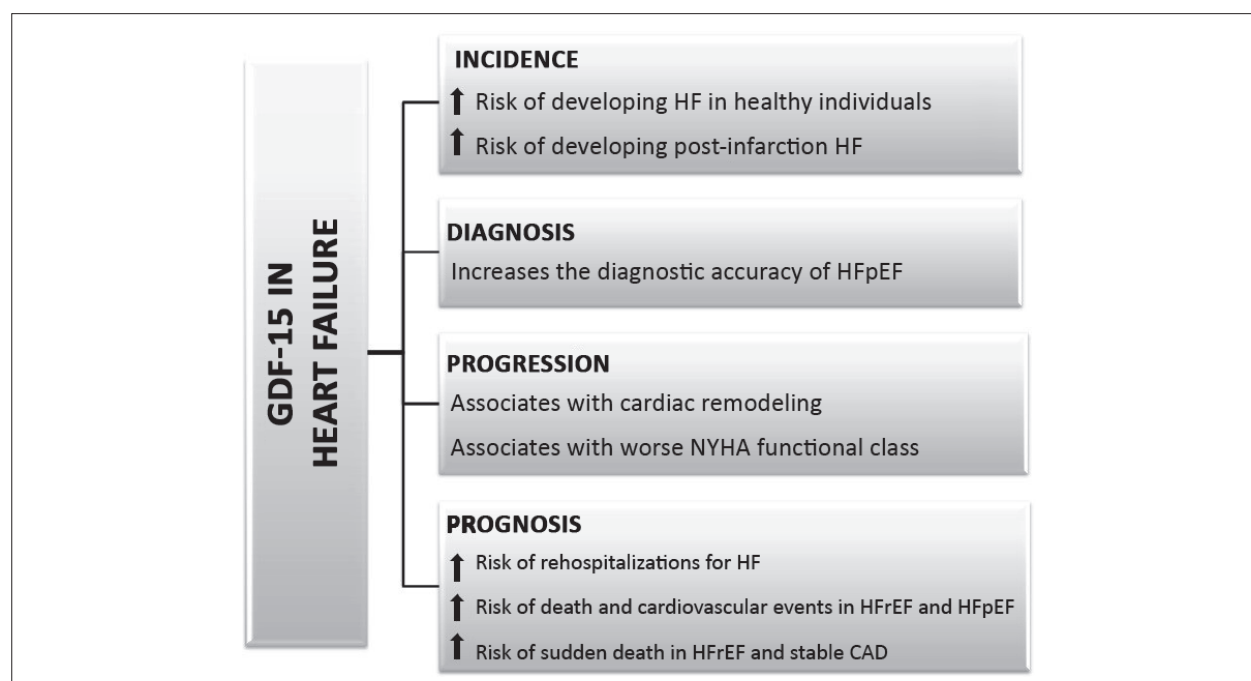


Figure 2 – Implications of increased growth differentiation factor-15 (GDF-15) levels in different clinical conditions of heart failure; HF: heart failure; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; NYHA: New York Heart Association; CAD: coronary artery disease

Atrial Fibrillation (AF)

Among patients with atrial fibrillation, receiving adequate treatment and anticoagulation, those with elevated GDF-15 had four to five-fold higher mortality rate, independently of age, sex and CHA₂DS₂VASc.⁵⁰ A similar finding was seen in the study by Sharma et al.,⁵¹ where GDF-15 was strongly associated with death due to HF and bleeding.⁵¹

Nonanticoagulated nonvalvular AF patients with serum levels of GDF-15 above 809 ng/dL are at higher risk for developing left atrial thrombus, regardless of age, atrial volume, and CHA₂DS₂VASc.⁵²

In a study with 14,798 anticoagulated patients, those with elevated GDF-15 levels had a 3.5-fold increased risk of major bleeding, regardless of the antithrombotic therapy and other comorbidities.⁵⁰ After this finding, the ABC (age, biomarkers [GDF-15, hemoglobin and troponin], and clinical history)-bleeding risk score was developed and validated, and the GDF-15 was the biomarker that most contributed to the risk. The ABC bleeding score showed better accuracy than the HAS-BLED score, which is the most used score in clinical practice.⁵³

Chronic Renal Disease

Cardiac remodeling, fibrosis, and inflammation are possibly involved in the increase of cardiovascular events in patients with chronic renal disease (CRD).

Analysis of biomarkers possible representative of these conditions, the ST2, galectin-3 and GDF-15 were found to be significantly associated with mortality in these patients, but not with atherosclerotic events. Among these, only GDF-15 correlated with the risk of developing HF.⁵⁴

Similar results were found by Bansal et al.,⁵⁵ who reported that GDF-15 was a predictor of HF in patients with renal dysfunction, similarly to NT-proBNP. However, unlike the natriuretic peptide, the GDF-15 was more strongly correlated with HFpEF.⁵⁵

Patients with a glomerular filtration rate below 60 mL/min/1.73m² showed significantly higher levels of GDF-15 and NT-proBNP as compared with patients with normal renal function. In a cohort of 358 patients with CRD and systolic dysfunction, GDF-15 refined the prognostic stratification of patients with low NT-proBNP and was

more strongly associated with adverse events than the peptide itself.⁵⁶

Table 1 describes serum GDF-15 levels (mean) associated with the clinical conditions addressed in this review.

Conclusion

GDF-15 is a serum biomarker whose expression seems to be affected by stress, tissue damage, and inflammation, although its pathophysiological pathway has not been elucidated yet. Observational studies with healthy individuals have shown an association of GDF-15 with higher risk of cardiovascular events over time. In patients with coronary artery disease and HF, GDF-15 was correlated with increased risk of overall mortality and adverse events. The use of GDF-15 improved the diagnostic performance for detecting HFpEF and contributed to the development of a more accurate risk score to predict bleeding in AF. The use of GDF-15 as a prognostic marker in clinical practice and its capacity to guide the decision-making process still depends on new studies with larger samples.

Author Contributions

Conception and design of the research, Data acquisition and Analysis and interpretation of the data: May BM, Pimentel M; Writing of the manuscript and Critical revision of the manuscript for intellectual content: May BM, Pimentel M, Zimmerman LI, Rohde LE.

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No potential conflict of interest relevant to this article was reported.

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Study Association

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Table 1 – Cut-off points of growth differentiation factor-15 (GDF-15) used for diagnosis and prognosis in different clinical conditions (values in ng/L)

Diagnostic cut-off levels	Prediction of adverse events			
	Cardiovascular events	Cardiovascular death	Sudden death	Overall mortality
HF with reduced ejection fraction ^{7,33,34}	> 1,200	> 2,040	> 2,252	*
HF with preserved ejection fraction ^{31,40,42}	> 1,160	*	NA	NA
Acute coronary syndrome ^{15,19}	> 967	> 1,550	> 1,550	NA
Stable coronary artery disease ²⁷	NA	> 1,253	> 1,827	> 1,253

NA: Not accessible (no study including the outcome, or unreliable, small studies). * Use of growth differentiation factor-15 (GDF-15) as a continuous variable, without specific cut-off point.

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What are the Optimal Reference Values for Home Blood Pressure Monitoring?

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Introduction

The diagnosis of hypertension usually relies on office blood pressure (BP) measures. However, this approach might underestimate or overestimate the true prevalence of hypertension due to the presence of alternative BP phenotypes, such as masked hypertension and white-coat hypertension. In this regard, current hypertension guidelines have recommended the evaluation of out-of-office BP by ambulatory BP monitoring (ABPM) or home blood pressure monitoring (HBPM), when these techniques are available, to confirm the diagnosis and to provide a more adequate management of hypertension.¹⁻⁴

HBPM reference values used to define hypertension have been more consistently suggested since the end of 1990s. In 1998, results of a meta-analysis including data from 17 studies and 5,422 untreated participants suggested that elevated HBPM values should be $\geq 137/89$ mmHg or $\geq 135/86$ mmHg based on analysis of means + 2 standard deviations or ninety-fifth percentiles, respectively.⁵ In 1999, the analysis of the ninety-fifth percentiles of HBPM values from 2,401 normotensive individuals at the office estimated that elevated HBPM values were $\geq 137/85$ mmHg.⁶ Furthermore, the evaluation of 1,913 individuals (69% not

treated with antihypertensive medications) from the Ohasama Study showed that HBPM values $\geq 137/84$ mmHg were associated with greater risk of death after 5 years of follow-up.⁷ Subsequent hypertension guidelines rounded the reference values suggested by these latter studies and recommended that abnormal HBPM measures should be considered when $\geq 135/85$ mmHg.^{8,9} HBPM thresholds of 135/85 mmHg were then incorporated into clinical practice, and they have been used to define abnormal HBPM values by hypertension guidelines from various societies,^{3,10} including the Seventh Brazilian Hypertension Guidelines published in 2016¹ and the Sixth Brazilian Guidelines of ABPM and Fourth Brazilian Guidelines of HBPM published in 2018.⁴

Several reports published in the last decade evaluating individuals not using antihypertensive medications have suggested that HBPM reference values used to define hypertension should be reviewed.¹¹⁻¹⁴ In 2012, Coll-de-Tuero et al. reported that HBPM values $< 130/80$ mmHg were associated with lower risk of development of end-organ damage than HBPM values $< 135/85$ mmHg in a sample of 466 individuals.¹¹ In 2017, a Korean study evaluating 256 participants found that HBPM values $\geq 130/80$ mmHg had greater accuracy than HBPM values $\geq 135/85$ mmHg to detect hypertension, considering ABPM measurements as a reference.¹² More recently, in 2020, results of regression analysis including 9,868 untreated Brazilian participants showed that office BP values of 140/90 mmHg corresponded to HBPM values of 130/82 mmHg.¹³ Regarding long-term outcomes, Niiranen et al.¹⁴ published, in 2013, a meta-analysis including data from 5,018 untreated individuals from 5 countries, which showed that HBPM values of 131.9/82.4 mmHg were equivalent to office BP values of 140/90 mmHg in predicting cardiovascular events.¹⁴ Overall, these studies demonstrated that normal HBPM values are actually closer to 130/80 mmHg than 135/85 mmHg, thus providing support for changing HBPM reference values from 135/85 mmHg to 130/80 mmHg.

Keywords

Hypertension; Blood Pressure; Reference Values; Reference Standards; Blood Pressure Self-Monitoring.

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Numerous reports evaluating individuals using antihypertensive medications have also indicated that HBPM values lower than 135/85 mmHg are more adequate to define the presence of high BP levels.^{13,15-17} Results of regression analysis including data from 10,069 treated Brazilian participants showed that HBPM values of 131/82 mmHg were equivalent to office BP values of 140/90 mmHg.¹³ The evaluation of 700 treated hypertensive patients from the Ohasama Study demonstrated that the incidence of stroke was greater in patients with HBPM values ranging between 125/80 and 134/84 mmHg than in those with HBPM values < 115/75 mmHg after a mean follow-up of 11.9 years, indicating that patients with HBPM values lower than 135/85 mmHg might still have greater risk of adverse cardiovascular events.¹⁵ In another study evaluating 3,518 treated Japanese patients, Asayama et al.¹⁶ found that individuals who achieved systolic HBPM values lower than 131.6 mmHg had lower risk of presenting adverse cardiovascular outcomes.¹⁶ Recently, Colde-Tuero et al.¹⁷ reported that, among treated patients with high office BP levels but no sign of end-organ damage, those with HBPM values < 130/80 mmHg had mortality similar to individuals with normal office BP levels, while individuals with HBPM values < 135/85 mmHg had greater mortality.¹⁷ In general, these data obtained in treated hypertensive patients provide additional support to the idea that HBPM $\geq$ 130/80 mmHg should be used to define individuals with elevated BP levels.

Finally, we believe it is worth mentioning that HBPM and daytime ABPM should not be considered as equivalent measures. Daytime ABPM measures BP while the studied individuals are performing their regular activities at work, in transportation, or during meals and when they are at rest or under stress. Conversely, HBPM values are derived from a strict protocol where the studied individuals measure their BP in a quiet environment, after at least 3 minutes of rest, in the morning and in the evening, before using antihypertensive medications or having meals (or 2 hours after dinner), and with empty bladder. In this context, it is common that daytime ABPM values are slightly greater than HBPM values.¹⁸ Therefore, it can be stated that daytime ABPM and HBPM are distinct measures, and they may have different reference values.

Conclusion

Based on the aforementioned evidence, the Brazilian Guidelines of Hypertension 2020¹⁹ recommend that HBPM values should be considered abnormal when they are greater

or equal to 130/80 mmHg, thus substituting the previous thresholds ($\geq$ 135/85 mmHg) recommended by the Seventh Brazilian Hypertension Guidelines,¹ the Sixth Brazilian Guidelines of ABPM, and the Fourth Brazilian Guidelines of HBPM.⁴

Author Contributions

Conception and design of the research: Feitosa ADM, Mota-Gomes MA, Nobre F, Mion Jr. D, Paiva AMG, Argenta F, Barroso WKS, Miranda RD, Barbosa ECD, Brandão AA, Jardim TSV, Jardim PCBV; Writing of the manuscript: Feitosa ADM, Nadruz W; Critical revision of the manuscript for intellectual content: Mota-Gomes MA, Nobre F, Mion Jr. D, Paiva AMG, Argenta F, Barroso WKS, Miranda RD, Barbosa ECD, Brandão AA, Jardim TSV, Jardim PCBV.

Potential Conflict of Interest

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Study Association

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Early vs. Late Neutrophil-To-Lymphocyte Ratio for the Prediction of Adverse Outcomes in Patients with STEMI Undergoing Primary PCI

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Introduction

Admission neutrophil-to-lymphocyte ratio (NLR) has proven to predict adverse events in patients with ST-elevation Myocardial Infarction (STEMI).¹⁻³ New evidence has shown that NLR continues to increase within 48-72 hours in patients who develop worse outcomes.⁴ Therefore, this study sought to compare the prognostic capacity of admission and late NLR for adverse events in patients with STEMI undergoing primary percutaneous coronary intervention (pPCI).

Methods

This was a prospective cohort study with consecutive patients admitted with STEMI, who underwent pPCI and were followed up for 12 months. NLR was calculated by dividing the neutrophil count by the lymphocyte count obtained from the same blood sample. NLR was assessed at admission and 48-72 hours post-procedure (late NLR), as a part of routine care. Other details about procedural information, data collection, clinical definitions, exclusion criteria, and ethical guidelines are described elsewhere.² High NLR was defined as above upper tertile. Receiver operating characteristic (ROC) curve analysis was performed to calculate the area under the curve (AUC) for the occurrence of short and long-term mortality and major adverse cardiovascular events (MACE). Multivariate analysis was performed by Poisson robust regression to evaluate the independent predictive value of late NLR. For the multivariate model, risk factors that were univariate predictors (at $p < 0.05$) were initially considered factors or covariates. C-statistic analyses were compared with the De Long test, while Kaplan-Meier methods were compared with log-rank tests, performed using the MedCalc Statistical Software version 14.8.1 (MedCalc Software, Ostend, Belgium). All remaining statistical analyses were conducted using SPSS Statistics for Windows, v.21.0. (IBM Corp., Armonk, New York, USA).

Keywords

Myocardial Infarction; Angioplasty; Mortality; Neutrophil-to-lymphocyte Ratio; Inflammation; Risk Factors.

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Results

Between March 2011 and December 2018, 864 patients were admitted to our institution, diagnosed with STEMI, and 779 were included in the analysis. Mean age was 60.68 (± 12), 66.4% were male, 62.1% had hypertension, and 24% had diabetes.

In a multivariate analysis, when adjusted by age, pain-to-door time, previous chronic kidney disease, previous myocardial infarction (MI), hypotension at admission, femoral access, fluoroscopy time, contrast volume thrombolysis in myocardial infarction (TIMI) score, left ventricle ejection fraction $\leq 40\%$ before discharge, late NLR remained an independent predictor of in-hospital death, in-hospital MACE, and one-year mortality (relative risk [RR] = 14.9, 95% confidence interval [95% CI] = 3.4 - 80.35, $p = 0.001$; RR = 3.4, 95% CI = 1.2 - 9.1, $p = 0.01$; RR = 7.6, 95% CI = 2.9 - 26.1, $p = 0.01$, respectively). The use of late NLR increased significantly the AUC of in-hospital mortality from 0.55 to 0.84 (Sensitivity 81.2%, Specificity 75.6%, Positive Predictive Value 24.5, and Negative Predictive Value 97.7). Discriminative data of other outcomes are described in Figure 1. At the end of a one-year follow-up, the rate of death from any cause was 28.6% in the high late NLR group, hazard ratio [HR] = 3.07 (95% CI = 1.9 - 4.8); $p < 0.0001$; Figure 2).

Discussion

In this present cohort-based study of STEMI patients undergoing pPCI, late NLR was strongly associated with short and long-term mortality and MACE. Moreover, late NLR increased the admission NLR's prognostic capacity for adverse events in these patients. To the best of our knowledge, this was the first time late NLR was consistently evaluated in this setting.

Normal distribution of NLR is still a matter of debate. Forget et al.⁵ have studied healthy individuals and values ranged between 0.78 and 3.5, remaining stable after 48 hours. Recently, Kim et al.⁶ observed that NLR increases over time in individuals with cardiovascular disease, reaching peak values around the time of an adverse event. A recent study showed that patients who experienced adverse outcomes during follow-up had an acute increase in NLR values 48h after the procedure.⁴ These results support the findings of Kim et al.⁶ described above.

In the present study, when late NLR values were used to assess the ability to predict adverse events, there was a significant increase in AUC when compared to admission NLR. This might be explained because neutrophils are the first leukocytes to infiltrate the infarcted myocardium, releasing a

Research Letter

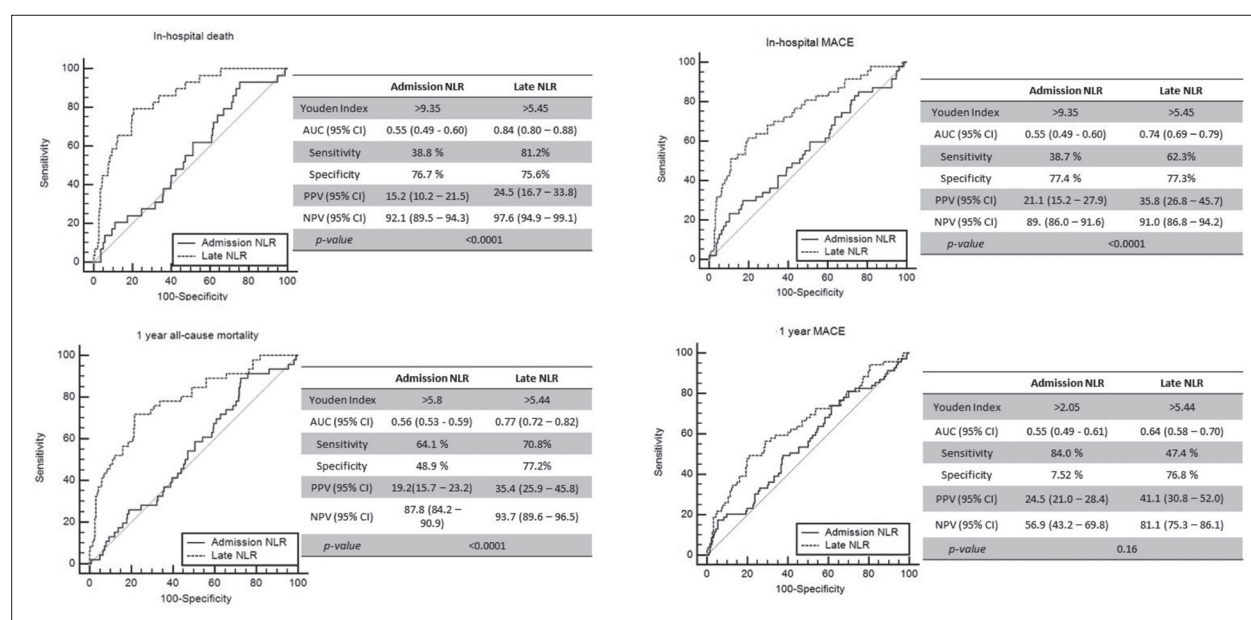


Figure 1 – Receiver operator characteristic (ROC) graph showing areas under the curve (AUC) of admission neutrophil-to-lymphocyte ratio (NLR) and late NLR for (A) in-hospital death, (B) in-hospital major cardiovascular outcomes (MACE), (C) one-year all-cause mortality, and (D) one-year MACE

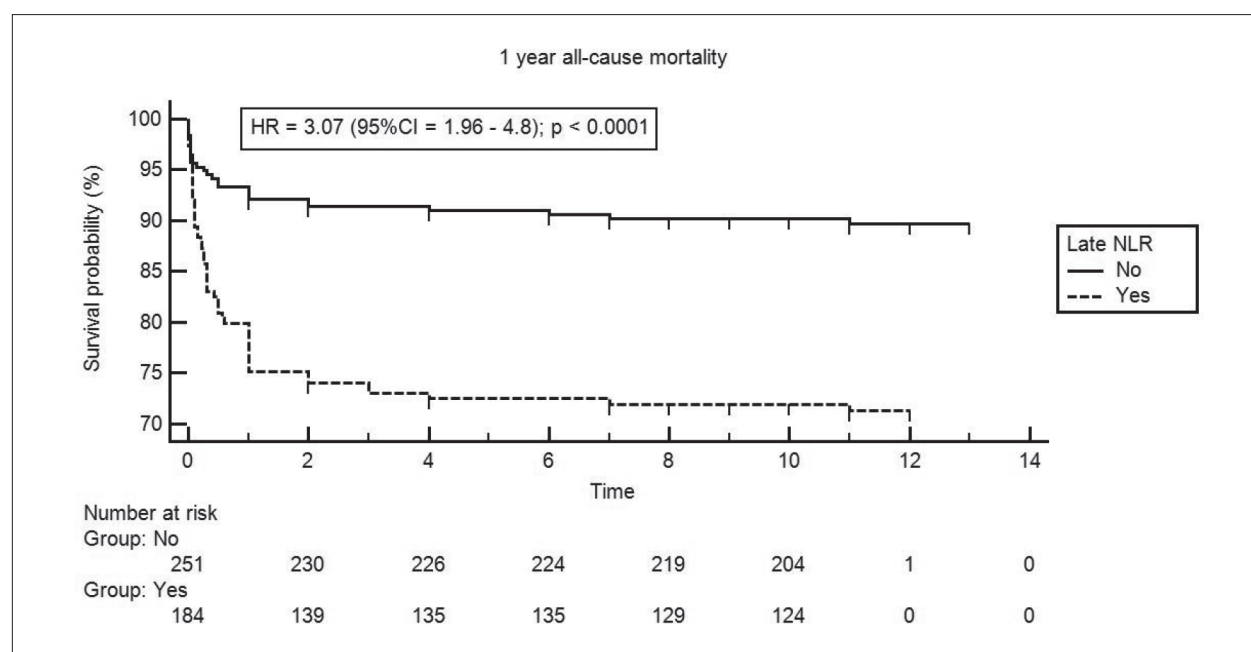


Figure 2 – Time-to-Event Curves for one-year all-cause mortality for late neutrophil-to-lymphocyte ratio (NLR). Event rates were calculated by means of Kaplan-Meier methods and compared with the use of the log-rank test

variety of proteolytic enzymes which cause plaque rupture, infarct expansion, coagulation pathway activation, and cardiac electrical instability.⁷⁻⁹ In addition, there is evidence of the prolongation of the lifespan of neutrophils in unstable plaques.¹⁰ In contrast to increased neutrophils in the damaged myocardial area, lymphocytes decrease due to increased levels of cortisol, catecholamines, and proinflammatory cytokines

in acute STEMI.^{11,12} This suggests that the exacerbated inflammatory response after the event defines the worse outcome for these patients.

In the clinical practice of most centers worldwide, white blood counts are routinely obtained during hospitalization for an acute coronary event. In the present study, a measurement of 48-72h NLR was a strong predictor of adverse outcomes,

which highlights a potential application of this inexpensive and readily available inflammatory marker for risk stratification of post-myocardial infarction.

Author contributions

Conception and design of the research: Machado GP, Maltauro D, Custodio J, Milan V; Data acquisition: Maltauro D, Custodio J, Milan V; Analysis and interpretation of the data and Statistical analysis: Machado GP, Araujo GN; Writing of the manuscript: Machado GP, Araujo GN, Wainstein M; Critical revision of the manuscript for intellectual content: Araujo GN, Wainstein M.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital de Clinicas de Porto Alegre under the protocol number 2018/0436. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.



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Three-Dimensional-Printed Heart Prototype for Application in Pediatric Cardiology: An Initial Experiment

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Introduction

Three-dimensional (3D) prototyping technology is developing rapidly in medicine, and recent studies have shown its important applicability in pediatric cardiology.

Clinicians and surgeons use two-dimensional technologies, such as echocardiography, computed tomography (CT) angiography, and magnetic resonance imaging, to characterize structures and understand complex diseases. Because these images are often projected and extended on a flat screen, they may not represent the actual size of the structures, depth perception, or the proximity between them.¹

The prevalence of congenital heart disease is estimated at 9.1 per 1000 live births.² It causes significant hemodynamic and functional consequences and accounts for 6% of all infant deaths in the first year of life in Brazil.³ The diversity and complexity of heart diseases require surgeons to have a detailed understanding of anatomy for proper treatment planning and management and for providing a didactic explanation of the disease to family members.^{4,5}

This study produced 3D-printed prototypes of congenital heart diseases from CT angiography image files as an initial experiment to increase scientific evidence.

Methods

We conducted a descriptive observational study without the application of a numerical comparison tool. The study aimed to present our initial experience based on current evidence of the use of 3D technology and its benefits in understanding congenital heart diseases and their importance in our setting. Representative images of heart diseases were obtained from CT angiography image files and chosen among those of greater anatomical complexity in order to obtain better structural information with 3D printing. The selected

heart diseases were pulmonary atresia with ventricular septal defect (PA-VSD) and systemic-to-pulmonary collaterals, and left ventricular hypoplasia (LVH) after ductus arteriosus stenting and cerclage of the branch pulmonary arteries. The images were obtained with a GE Revolution 512-slice CT scanner with electrocardiographic modulation and imported into Slic3r for structural segmentation. The prototypes were printed in a ZMorph VX/E 3D printer using 0.2-mm-thick polylactic acid thermoplastic filaments and PVA support. After printing, the 3D prototypes were visually compared with the CT angiography images by the authors.

Results

Visual comparison of the CT angiography images with 3D-printed prototypes showed anatomical compatibility between them, and important anatomical details could be observed from different perspectives in the 3D prototypes. In the PA-VSD case, the 3D-printed prototype facilitated the understanding of the spatial relationship between the systemic-to-pulmonary collaterals originating from the aorta and the branch pulmonary arteries, as well as the comparative observation of the ventricular cavities (Figure 1). In the LVH case, we could observe the degree of hypoplasia of the ascending aorta and the presence of branch pulmonary artery stenosis, in addition to the spatial relationships between them (Figure 2). The size of the 3D models corresponded to the anatomy of the patients, enabling a comparative study of the dimensions between the structures, which may contribute to the surgical treatment strategy. The possibility of having a hands-on 3D prototype to observe the anatomy from different angles allowed an easier and clearer understanding of heart diseases.

Discussion

Three-dimensional printing is a technology that aims to complement conventional tests, since it provides greater understanding of cardiac malformation. It allows a detailed study of the location, length, extension, and relationship between the malformed structures, thus assisting in surgical planning and in identifying anatomical details of patients who have undergone previous interventions.⁶ Consequently, it benefits surgeons by increasing their knowledge of the heart disease and by providing a greater degree of safety when choosing the surgical technique.⁷ Studies of patients with PA-VSD have shown that 3D prototypes enable the visualization of 96% of the major aortopulmonary collateral arteries compared with intraoperative assessment. Thus, it focuses

Keywords

Heart Defects Congenital; Coronary Angiography/methods; TomographyX-Ray Computed/methods; PrintingThree-Dimensional/trends.

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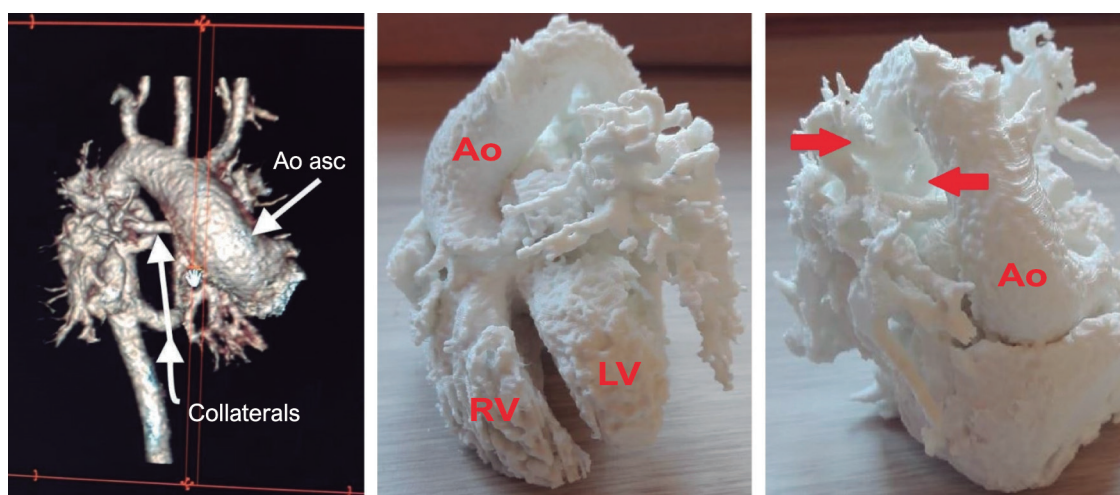


Figure 1 – PA-VSD case. Left: CT angiography: arrows indicate the aorta and the presence of systemic-to-pulmonary collateral arteries emerging from the ascending aorta. Right: 3D prototype – front and right-side view. Ao: aorta; LV: left ventricle; RV: right ventricle.

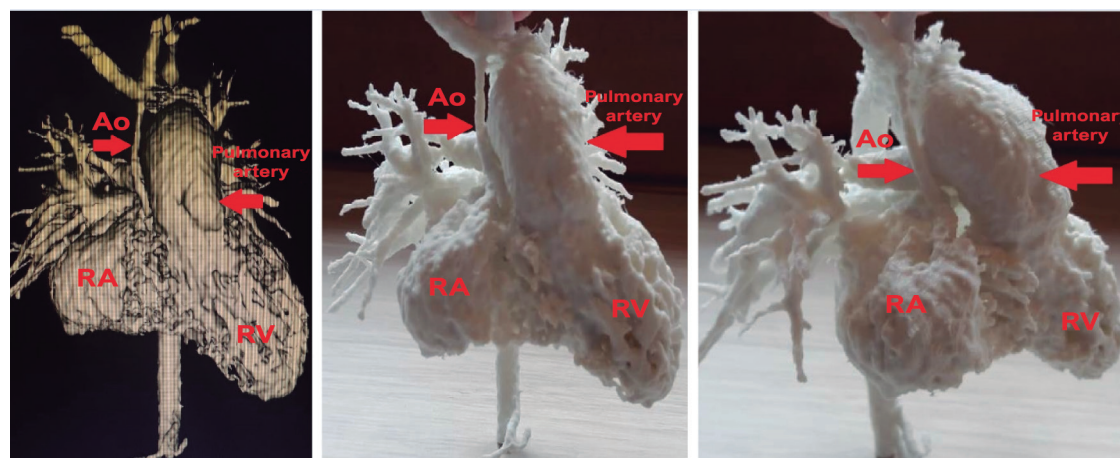


Figure 2 – LVH case. Left: CT angiography – arrows indicate the aorta and pulmonary artery. Right: 3D prototype – lateral view. Ao: aorta; RA: right atrium; RV: right ventricle.

on catheterization and reduces operative time, exposure to anesthesia, fluid therapy time, and the use of contrast agents in hemodynamic procedures.⁶⁻⁸

The 3D prototypes can also be used for surgical simulations, aiming to anticipate the need for adjustments to the surgical plan, to reduce complications, to obtain good postoperative results, and to train students and physicians.¹ Some 3D prototypes are highly flexible and do not require special handling; therefore, they can be used both before and during surgery.⁹

In medical education, 3D printing allows medical students and residents to better understand the pathology and spatial orientation of the structures. With the growing difficulties in obtaining cadavers for study, the use of 3D prototypes is an important option for the teaching of human anatomy in medical schools.¹⁰

In the context of the doctor-patient relationship, the possibility that parents may hold the prototype in their own hands and visualize the anatomical details described by the physician provides a better understanding both of the pathophysiology related to the patient's symptoms and of the proposed treatment. The literature shows that 3D prototypes help to strengthen the doctor-patient relationship, are useful in understanding information, and increase the knowledge and engagement of patients and families in relation to the disease.¹¹

Three-dimensional printing is a developing technology that has limitations and challenges to ensure a better-quality product, including assembly accuracy, construction of models with the same mechanical properties of the tissues, shorter preparation time, and lower economic cost. The possibility of printing different colors would facilitate the identification of different types of structures, such as ventricles, pulmonary

Research Letter

artery and branches, and aorta, especially in undergraduate medical education.

The heart diseases represented by our 3D prototypes provided reliable 3D representations of the CT angiography images used as a basis for the study. Producing 3D-printed heart prototypes is feasible and can be a useful tool in our setting, as they can be used to assist clinicians and surgical teams in treatment decision-making, students' learning in undergraduate and graduate medical education, and surgical-skill education and to provide explanations to family members about the child's heart disease.

Note: in the publication of this manuscript, it must be taken into account that the visual effect of the 3D prototypes is reduced on photographs, compared with the direct, actual handling of the product.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Basso ML, Farah MCK; Data acquisition, Analysis and interpretation of the

data and Writing of the manuscript: Gebran AM, Oliveira JD, Gebran KM, Bonatto LC.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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Serum Levels of BDNF in Cardiovascular Protection and in Response to Exercise

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Dear Editor,

I read with interest the article published by Trombetta et al.¹ In this sense, the importance of disseminating new markers in cardiovascular disease is increasingly known. I bring to the discussion a protein called growth factor / differential 15 (GDF-15) that was first identified as cytokine 1 or MIC-1 of the TGF-

beta family, it has pleiotropic effects depending on the model being studied.² The interesting thing about this discussion is the interface with which the Brain-derived neurotrophic factor (BDNF) interacts with the GDF-15 molecule, which also has effects on the vascular system, but in high concentrations it can present an adverse response, considered an independent prognostic marker for the cardiovascular disease there is evidence that physical exercise controls serum GDF-15 levels, protecting us from heart/coronary diseases, metabolic diseases, and oncological diseases.^{2,3} In this context, BDNF is also a prognostic marker in cardiovascular disease with function beyond the brain receptor in order to promote the maturation of GDF-15.⁴ According to the theoretical rationale, the proprotein convertase subtilisin/kexin 9 (PCSK-9) presents in its constitution a triad with an amino acid sequence (Asp-His-Ser) with a catalytic function that promotes cleavage of GDF-15 and maturation to the intracellular medium.⁴ Evidence shows that GDF-15 precursors that are not cleaved and in large amounts in the extracellular matrix correlate with an increased risk of a worse clinical outcome in heart failure.⁴

Keywords

Cardiovascular Diseases/mortality; BDNF; Brain-Derived Neurotrophic Factor; Endothelium Vascular; Nerve Growth Factors; Polymorphism; Exercise.

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Acute Myocardial Infarction with Coronary Thrombosis in a Covid-19 Patient without Risk Factors for Cardiovascular Disease

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Case Report

A 32-year-old young man, without cardiovascular risk factors, sought an Emergency Unit due to severe chest pain 30 minutes before admission, without irradiation. Admission vital signs: T 36.1°C, heart rate of 89 bpm and peripheral O₂ saturation of 96% in room air. During systematic interrogation, anosmia and ageusia were reported two days ago and fever or any other respiratory symptom was denied.

He was previously healthy and denied use of illicit drugs or previous history of angina. He denies a family history of acute myocardial infarction or coronary artery disease.

The 12-lead electrocardiogram (EKG) showed ST segment elevation in DII, DIII and aVF; and depression in DI and aVL, compatible with acute myocardial infarction with ST-segment elevation (STEMI) of the inferior wall (Figure 1) and positive troponin. Other laboratory tests showed changes in C-reactive protein of 6.7 mg/L (VR: <10mg/L), ferritin 350.2 ng/mL (VR: 21.8 to 274.6 ng/mL), LDH 5600 U/L (VR: 120 to 246 U/L) and leukocytosis of 12,450 cell/uL. Ultra sensitive troponin was above 50 ng/mL (VR: <0.034 ng/mL).

The patient received an attack dose of dual antiplatelet therapy (aspirin 300 mg and clopidogrel 300 mg). As referral to angioplasty in less than 120 minutes would not be possible, fibrinolytic therapy was used, using Tenecteplase (delta T of 5 hours and 36 minutes). The post-thrombolysis EKG showed a 50% reduction in elevation of the ST segment, but the patient persisted with chest pain. Considered a failure of reperfusion, the patient was referred for rescue angioplasty. Cineangiogram (Figure 2; video 1 and 2) revealed a right coronary artery with a large burden of thrombus in the middle and distal segment, without obstructive atherosclerotic lesions in other coronaries. Due to the high thrombotic load, despite

the reduced flow (TIMI 2), it was decided not to intervene and to use dual antiplatelet therapy associated with low molecular weight heparin in a therapeutic dose for 72 hours. The patient was transferred to the intensive care unit with complete symptom relief.

COVID-19 was suspected, a nasopharyngeal swab was performed using RT-PCR for SARS-COV2, which was positive. Computed tomography of the chest, without changes. No specific therapy was instituted for COVID-19, as the patient remained without respiratory symptoms.

The patient was discharged after four days, with total relief of angina, using aspirin, apixaban and enalapril. After fifteen days, he remained asymptomatic and underwent coronary computed tomography angiography that showed a residual thrombus in the middle third of the right coronary artery with a slight luminal reduction and a patent distal bed (Figures 3 and 4).

Discussion

The COVID-19 infection was declared a pandemic by the World Health Organization in March 2020, being responsible for high morbidity and mortality in several countries around the world. When symptomatic, the infection most commonly presents with symptoms of the respiratory or gastrointestinal tract, which may be associated with cardiovascular manifestations, from myocardial injury to acute myocardial infarction, fulminant myocarditis and cardiogenic shock, increasing the morbidity and mortality of the disease.¹

Previous studies have shown that patients with COVID-19 are predisposed to thromboembolic events, both venous and arterial, including peripheral and pulmonary thromboembolism, stroke, acute myocardial infarction and acute lower limb ischemia.²⁻⁴

The patient described is a young man with no risk factors for coronary artery disease, who had an episode of inferior STEMI with a high thrombotic burden without evidence of atherosclerotic disease in other coronary arteries and with positive RT-PCR for COVID-19. As he is a patient without other known risk factors for coronary thrombosis, it is likely that viral infection and the inflammatory response are the protagonists in the activation of the coagulation cascade as the cause of coronary thrombosis with clinical manifestation of acute myocardial infarction.

Seif et al.,⁵ Dominguez-Erquicia et al.⁶ and Al-Sadawi et al.⁷ described cases of patients without risk factors for coronary artery disease (CAD) who had STEMI and coronary angiography showing massive thrombus with occlusion coronary artery disease without associated atherosclerotic

Keywords

Myocardial Infarction; COVID-19; Betacoronavirus; Young Adult; Coronary Thrombosis; Thrombolytic Therapy.

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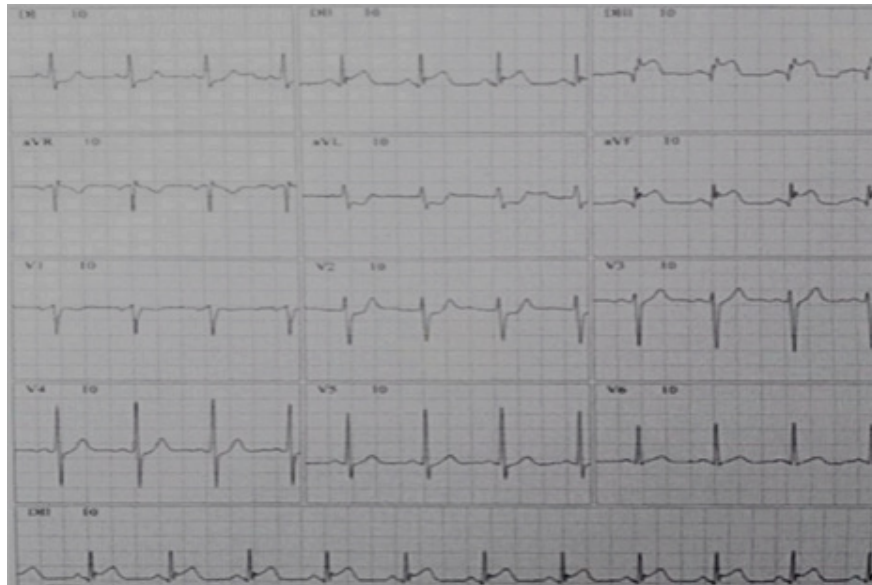


Figure 1 – Eletrocardiogram of the admission. Electrocardiogram revealed ST segment elevation in II, III and aVF and ST-segment depression in I and aVL, compatible with inferior acute myocardial infarction.

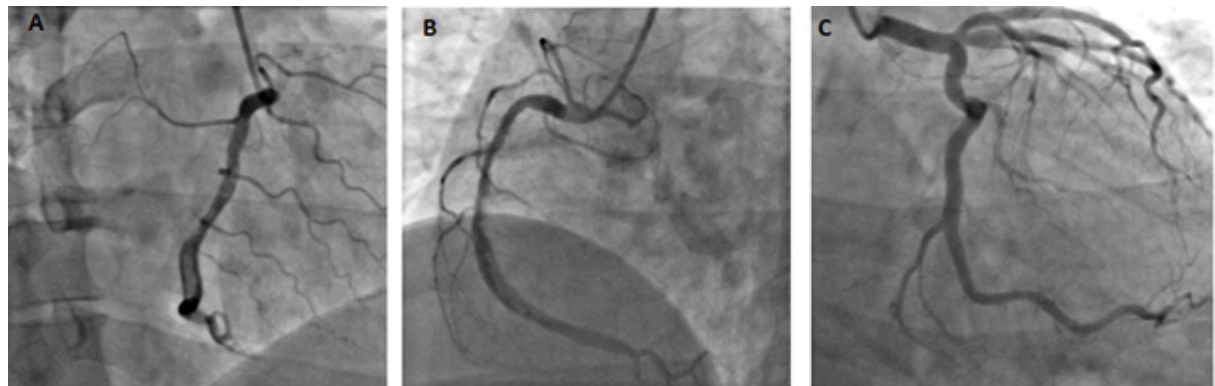


Figure 2 – Coronary angiography. (A) Right coronary with a large BURDEN of thrombus in its medial and (B) distal portions. (C) Left coronary artery without atherosclerotic lesions.

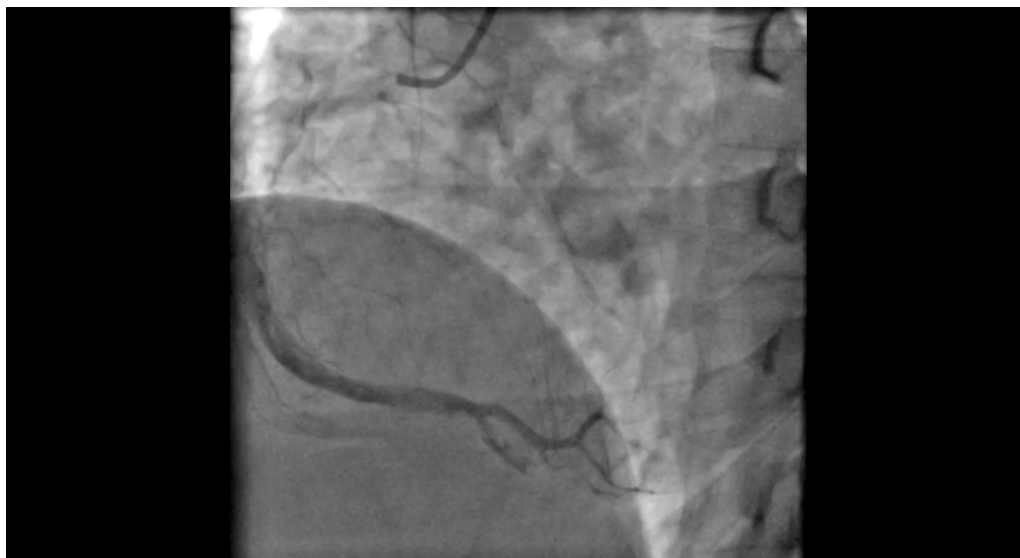
disease. Since these are patients without risk factors for CAD and without coronary atherosclerotic plaques, raises the possibility that the thrombotic event is associated with the hypercoagulable state of COVID-19 infection. In these and in the case described by Lacour et al.,⁸ coronary thrombosis was not associated with severe acute respiratory syndrome, reinforcing the possibility of thrombotic events even in patients without severe respiratory or systemic manifestations.

Similar to previously reported cases,^{5,7} this case describes a patient with COVID-19 and STEMI presenting high thrombotic burden on coronary angiography and absence of reperfusion criteria after fibrinolytic therapy, revealing the need for early rescue percutaneous intervention therapy. The large burden of thrombus should encourage the

use of more aggressive pharmacological therapy, such as fibrinolytics, glycoprotein IIb/IIIa inhibitor and prolonged use of anticoagulants. The use of anticoagulant associated with antiplatelet therapy for a few weeks after the event should be considered due to the prothrombotic state associated with COVID-19 infection.

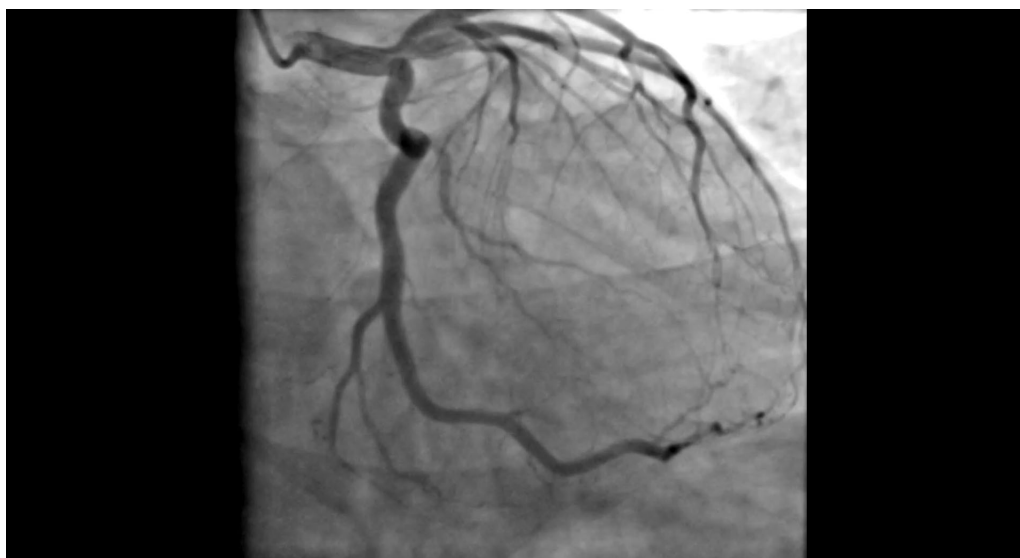
The use of coronary angiotomography to monitor the lesion in this case reinforces the possibility of a non-invasive coronary study allowing the evaluation of the plaque in addition to luminography. In addition, in the context of the COVID-19 pandemic, the performance of angiotomography reduces exposure and risks for the health team, allowing, when necessary, assessment of pulmonary changes in conjunction with coronary assessment.⁸

Image



Video 1 – Angiography of the right coronary. The coronary angiography revealed a right coronary artery with a large burden of thrombus in extensive mid and distal segment.

Link: <http://abccardiol.org/supplementary-material/2021/11603/2020-0972-Video01.mp4>



Video 2 – Left coronary angiography. Coronary angiography without evidence of atherosclerotic obstructive lesion in the other coronary arteries.

Link: <http://abccardiol.org/supplementary-material/2021/11603/2020-0972-Video02.mp4>

Conclusion

Acute myocardial infarction with coronary thrombosis is an entity that can be associated with COVID-19 due to the prothrombotic state predisposed by the infection, even in patients without known cardiovascular risk factors. In these cases, in view of the high thrombotic burden, aggressive pharmacological therapy

should be considered, instead of angioplasty.

Author contributions

Conception and design of the research: Viana T, Melo RMV, Bezerra CG; Data acquisition: Viana T, Bezerra MLBG, Bezerra CG, Mamédio V, Dourado GP; Analysis and interpretation of

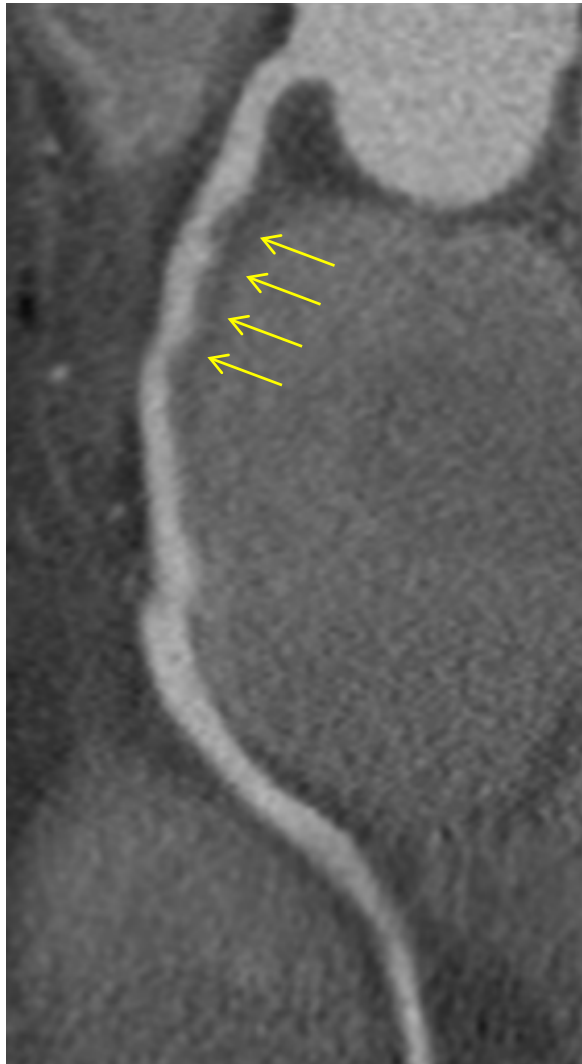


Figure 3 – Follow-up coronary angiotomography. Coronary angiotomography showing images suggestive of residual thrombi (arrows) in the proximal-middle third of the right coronary, with slight luminal reduction and a patent distal bed.

the data: Bezerra MLBG; Writing of the manuscript: Viana T, Mamédio V, Dourado GP; Critical revision of the manuscript for intellectual content: Bezerra MLBG, Melo RMV, Bezerra CG.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

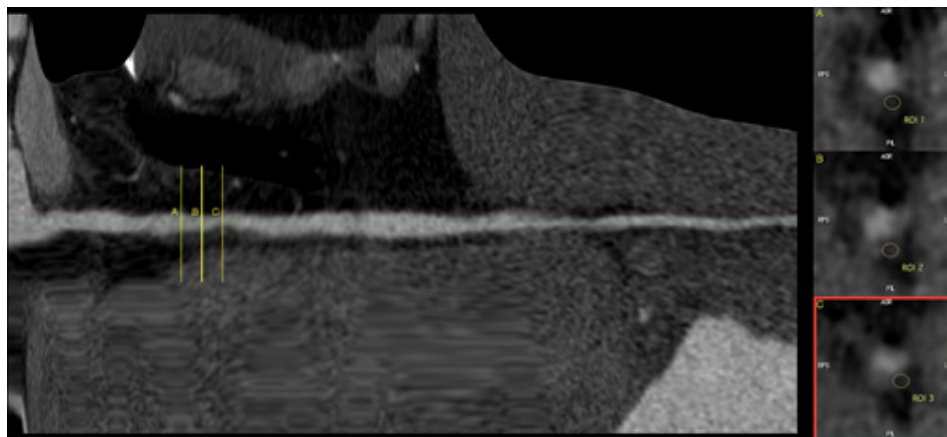


Figure 4 – Follow-up coronary angiotomography. Right Coronary Artery with irregular and segmental luminal narrowing of a slight degree in the proximal-middle third. In the transversal view of the vessel in the narrowing areas, images with low attenuation (20 to 100HU) are closely related to the vessel wall, which may be compatible with the hypothesis of thrombi.

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Note: These guidelines are for information purposes and should not replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

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Declaration of potential conflict of interests of authors/collaborators of the Brazilian Guidelines of Hypertension – 2020

If, within the last 3 years, the author/collaborator of the guideline:

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List of Abbreviations

ABI	ankle-brachial index	GBD	global burden diseases
ABPM	ambulatory blood pressure monitoring	GH	growth hormone
AC	arm circumference	GRS	global risk score
ACEI	angiotensin-converting enzyme inhibitor	GST	gait speed test
ADL	activity of daily living	HBP	high blood pressure
AE	adverse event	HBPM	home blood pressure monitoring
AF	atrial fibrillation	HC	hypertensive crisis
Aix	augmentation index	HDL	high-density lipoprotein
AMI	acute myocardial infarction	HE	hypertensive emergency
APA	aldosterone-producing adenomas	HELPP	hemolysis, elevated liver enzymes, low platelets
APE	acute pulmonary edema	HF	heart failure
ARB	angiotensin II AT1 receptor blocker	HFpEF	heart failure with preserved ejection fraction
ASA	acetylsalicylic acid	HFrEF	heart failure with reduced ejection fraction
BB	beta-blockers	HPLC	high-performance liquid chromatography
BE	blinding effect	HR	heart rate
BMI	body mass index	hs-TnT	high-sensitivity troponin T
BP	blood pressure	HT	hypertension
CAD	coronary artery disease	HTPC	hypertensive pseudocrisis
CCB	calcium channel blocker	HU	hypertensive urgency
cfPWV	carotid-femoral pulse wave velocity	ICU	intensive care unit
CGA	comprehensive geriatric assessment	IGF-1	insulin-like growth factor-1
CHW	community health worker	IV	intravenous
CKD	chronic kidney disease	LE	level of evidence
CO	cardiac output	LLs	lower limbs
CRP	C-reactive protein	LR	level of recommendation
CT	computed tomography	LSC	lifestyle change
CV	cardiovascular	MH	masked hypertension
CVD	cerebrovascular disease	MNR	magnetic nuclear resonance
CVD	cardiovascular disease	MOD	multi-organ damage
CVRF	cardiovascular risk factor	MS	metabolic syndrome
DALYs	disability-adjusted life years	NB	newborn
DBP	diastolic blood pressure	NCD	noncommunicable disease
DIU	diuretics	NE	norepinephrine
DM	diabetes mellitus	NIHSS	National Institute of Health Stroke Scale
EF	ejection fraction	NO	nitric oxide
eGFR	estimated glomerular filtration rate	NOO-	peroxynitrite
eNOS	endothelial nitric oxide synthase	NPT	nonpharmacological treatment
EOD	end-organ damage	NT-proBNP	N-terminal pro b-type natriuretic peptide
FMD	fibromuscular dysplasia	NTG	nitroglycerin
FMD	flow-mediated dilation	OH	orthostatic hypotension

Guidelines

OSA	obstructive sleep apnea	RHT	resistant hypertension
PE	pre-eclampsia	RVH	renovascular hypertension
PEF	preserved ejection fraction	SBP	systolic blood pressure
PHEO	pheochromocytoma	SHT	sustained hypertension
PNS	Brazilian National Health Survey	SMBP	self-measured blood pressure
PNS	parasympathetic nervous system	SNP	sodium nitroprusside
POAD	peripheral occlusive atherosclerotic disease	SNS	sympathetic nervous system
PPH	postprandial hypotension	SUS	Brazilian Unified Health System
PRA	plasma renin activity	T4	thyroxine
PVR	peripheral vascular resistance	TG	triglycerides
PWV	pulse wave velocity	TNT	true normotension
R/S	religiosity and spirituality	TSH	thyroid-stimulating hormone
RAAS	renin-angiotensin-aldosterone system	UAOBPM	unobserved automated office blood pressure measurement
RAS	renal artery stenosis	UN	United Nations
RCT	randomized controlled trial	WCE	white-coat effect
REF	reduced ejection fraction	WCH	white coat hypertension
RF	risk factors	WHO	World Health Organization
RfHT	refractory hypertension	YLL	<i>years of life lost</i>

Content

1. Definition, Epidemiology, and Primary Prevention	528
1.1 Definition of Hypertension.....	528
1.2. Impact of Hypertension on Cardiovascular Diseases.....	528
1.3. Risk Factors for Hypertension.....	528
1.3.1. Genetics.....	528
1.3.2. Age.....	528
1.3.3. Sex.....	528
1.3.4. Race/Ethnicity.....	528
1.3.5. Overweight/Obesity.....	528
1.3.6. Sodium and Potassium Intake.....	528
1.3.7. Sedentary lifestyle.....	529
1.3.8. Alcohol.....	529
1.3.9. Socioeconomic Factors.....	529
1.3.10. Other Risk Factors for High BP.....	529
1.3.11. Obstructive Sleep Apnea (OSA).....	529
1.3.12. Global Epidemiological Data.....	529
1.4. Prevalence of Hypertension in Brazil.....	529
1.5. Primary Prevention.....	530
1.5.1. Introduction.....	530
1.5.2. Weight Control (LR: I; LEE: A).....	530
1.5.3. Healthy Diet (LR: I; LE: A).....	530
1.5.4. Sodium (LR: I; LE: A).....	530
1.5.5. Potassium (LR: I; LE: A).....	530
1.5.6. Physical Activity (LR: I; LE: A).....	530
1.5.7. Alcohol (LR: IIA; LE: B).....	531
1.5.8. Psychosocial Factors (LR: IIB; LE: B).....	531
1.5.9. Dietary Supplements (LR: I to III; LE: A and B).....	531
1.5.10. Smoking (LR: I; LE: A).....	531
1.5.11. Spirituality (LR: I; LE: B).....	531
1.6. Strategies for the Implementation of Preventive Measures.....	531
2. Blood Pressure and Vascular Damage	535
2.1. Introduction.....	535
2.2. Blood Pressure, Clinical Outcomes, and Cardiovascular Damage.....	535
2.3. Blood Pressure, Inflammation, and Endothelial Dysfunction.....	536
2.4. Blood Pressure and Arterial Stiffness.....	536
2.4.1. Ankle-Brachial Index (ABI).....	536
2.4.2. Pulse Wave Velocity (PWV).....	537
2.4.3. Central Blood Pressure.....	537
3. Diagnosis and Classification	540
3.1. Introduction.....	540
3.2. Blood pressure measurement at the physician's office.....	540
3.3. Classification.....	540
3.4. Out-of-Office Blood Pressure Measurement.....	541
3.5. White-Coat Effect (WCE) and Masking Effect (ME).....	541
3.6. White Coat Hypertension (WCH) and Masked Hypertension (MH).....	541
3.7. Uncontrolled Masked and White Coat Hypertension.....	541
3.8. Diagnosis and Follow-Up Recommendations.....	541
3.9. Central Aortic Pressure.....	542
3.10. Genetics and Hypertension.....	542
4. Clinical and Complementary Assessment	548
4.1. Clinical History.....	548
4.2. Clinical Assessment.....	548
4.2.1. History-Taking.....	548
4.3. Physical Examination.....	548
4.3.1. Basic Laboratory Investigation, Assessment of Subclinical and Clinical End-Organ Damage.....	548
5. Cardiovascular Risk Stratification	552
5.1. Introduction.....	552
5.2. Additional Risk Stratification (Associated Conditions).....	552
5.2.1. End-Organ Damage.....	553
5.2.2. Presence of Cardiovascular and Renal Disease.....	553
5.3. Assessment of Global Cardiovascular Risk.....	553
5.4. Challenges of Cardiovascular Risk Assessment in Hypertension.....	553
6. Therapeutic Decision and Targets	556
6.1. Introduction.....	556
6.2. Low- or Moderate-Risk Hypertensive Patients.....	556
6.3. High-Risk Hypertensive Patients.....	556
6.4. Hypertensive Patients with Coronary Disease.....	556
6.5. Hypertensive Patients with History of Stroke.....	556
6.6. Hypertensive Heart Failure Patients.....	557
6.7. Hypertensive Patients with Chronic Kidney Disease (CKD).....	557
6.8. Diabetic Hypertensive Patients.....	557
6.9. Older Hypertensive Patients.....	557
7. Multidisciplinary Team	559
7.1. The Importance of a Multidisciplinary Approach to Hypertension Control.....	559
7.2. Team Composition and Work.....	559
7.2.1. Medical Professional: Specific Actions.....	559
7.2.2. Nursing Professional: Specific Actions.....	559
7.2.2.1. Nursing-Specific Actions in Primary Care.....	559
7.2.3. Nutrition Professional: Specific Actions.....	560
7.2.3.1. Dietetic Consultation.....	560
7.2.3.2. Collective Actions by Nutritionists.....	560
7.2.4. Physical Education Professional: Specific Actions.....	560
7.2.4.1. Collective Actions by Physical Education and Physical Therapy Professionals.....	560
7.3. Multidisciplinary Team Actions.....	561
8. Nonpharmacological Treatment	562
8.1. Introduction.....	562
8.2. Smoking.....	562
8.3. Dietary Patterns.....	562
8.4. Sodium Intake.....	563
8.5. Potassium.....	563
8.6. Dairy Products.....	563
8.7. Chocolate and Cocoa Products.....	563
8.8. Coffee and Caffeinated Products.....	563
8.9. Vitamin D.....	563
8.10. Supplements and Substitutes.....	564
8.11. Weight Loss.....	564
8.12. Alcohol Consumption.....	564
8.13. Physical Activity and Physical Exercise.....	564
8.14. Slow Breathing.....	565
8.15. Stress Control.....	565
8.16. Religiosity and Spirituality.....	565
9. Pharmacological Treatment	568
9.1. Treatment Objectives.....	568
9.2. General Principles of Pharmacological Treatment.....	568
9.3. Therapy Regimens.....	568
9.3.1. Monotherapy.....	568
9.3.2. Drug Combinations.....	568
9.4. General Characteristics of Different Classes of Antihypertensive Medications.....	569

Guidelines

9.4.1. Diuretics (DIUs)	569	13.2. Classification.....	596
9.4.1.1. Adverse Effects of Diuretics	569	13.3. Major Epidemiological, Pathophysiological, and Prognostic Aspects.....	596
9.4.2. Calcium Channel Blockers (CCBs)	569	13.3.1. Epidemiology	596
9.4.2.1. Adverse Effects of Calcium Channel Blockers.....	570	13.3.2. Pathophysiology	596
9.4.3. Angiotensin-Converting Enzyme Inhibitors (ACEIs).....	570	13.3.3. Prognosis	596
9.4.3.1. Adverse Effects of Angiotensin-Converting Enzyme Inhibitors	570	13.4. Complementary Clinical and Laboratory Investigation.....	597
9.4.4. Angiotensin II AT1 Receptor Blockers (ARBs)	570	13.5. General Treatment of Hypertensive Crisis.....	597
9.4.4.1. Adverse Effects of Angiotensin II AT1 Receptor Blockers.....	570	13.6. Hypertensive Emergencies in Special Situations	597
9.4.5. Beta-Blockers (BBs)	570	13.6.1. Hypertensive Encephalopathy.....	597
9.4.5.1. Adverse Effects of Beta-Blockers.....	571	13.7. Stroke.....	597
9.4.6. Centrally Acting Sympatholytics.....	571	13.7.1. Ischemic Stroke	597
9.4.6.1. Adverse Effects of Centrally Acting Sympatholytics	571	13.7.2. Hemorrhagic Stroke	598
9.4.7. Alpha-blockers.....	571	13.7.3. Acute Coronary Syndromes	598
9.4.7.1. Adverse Effects of Alpha-Blockers.....	571	13.7.4. Acute Pulmonary Edema (APE).....	598
9.4.8. Direct-Acting Vasodilators	571	13.7.4.1. Acute Aortic Dissection	598
9.4.8.1. Adverse Effects of Direct-Acting Vasodilators	571	13.7.5. Pre-eclampsia/Eclampsia.....	598
9.4.9. Direct Renin Inhibitors.....	571	13.7.6. HE from Illicit Drug Use.....	598
9.4.9.1. Adverse Effects of Direct Renin Inhibitors.....	572	13.7.7. Accelerated/Malignant Hypertension	598
9.5. Antihypertensive Drug Combinations.....	572	13.7.8. Hypertension with Multi-Organ Damage	599
10. Hypertension and Associated Clinical Conditions	578	14. Hypertension in Older Adults	602
10.1. Diabetes Mellitus (DM).....	578	14.1. Introduction.....	602
10.1.1. Treatment Objectives	578	14.2. Physiopathological Mechanisms	602
10.2. Metabolic Syndrome (MS)	578	14.3. Diagnosis and Therapeutic Decision.....	603
10.3. Coronary Artery Disease (CAD)	578	14.4. Treatment	603
10.4. Hypertension in Chronic Kidney Disease (CKD).....	578	14.4.1. Nonpharmacological Treatment.....	603
10.4.1. Patient in Conservative Treatment: Goals and Treatment.....	578	14.4.2. Pharmacological Treatment.....	603
10.4.2. Patients in Renal Replacement Therapy (RRT): Goals and Treatment	579	14.5. Special Situations	604
10.5. Heart Failure (HF)	579	14.5.1. Functional Status and Frailty: Assessment and Implications ...	604
10.6. Hemorrhagic Stroke and Ischemic Stroke	580	14.5.2. Cognitive Decline and Dementia	604
10.6.1. Hemorrhagic Stroke	580	14.5.3. Polypharmacy and Adherence.....	604
10.6.2. Ischemic Stroke	580	14.5.4. Deintensification and Deprescription	605
11. Hypertension in Pregnancy	581	14.5.5. Orthostatic and Postprandial Hypotension.....	605
11.1. Epidemiology	581	15. Secondary Hypertension	606
11.2. Classification of Hypertension in Pregnancy	581	15.1. Introduction.....	606
11.3. Concept and Diagnostic Criteria	581	15.2. Nonendocrine Causes	606
11.4. Prediction and prevention of pre-eclampsia	581	15.2.1. Chronic Kidney Disease (CKD)	606
11.5. Nonpharmacological treatment	582	15.2.2. Renovascular Hypertension (RVH).....	606
11.6. Expectant management.....	582	15.3. Fibromuscular Dysplasia	607
11.7. Pharmacological treatment.....	582	15.3.1. Coarctation of the Aorta	607
11.8 Future Cardiovascular Risk.....	583	15.3.2. Obstructive Sleep Apnea (OSA)	607
12. Hypertension in Children and Adolescents	586	15.3.2.1. Concept and Epidemiology.....	607
12.1. Epidemiological Context and Importance of Hypertension in Pediatrics	586	15.3.2.2. Clinical Presentation and Screening of OSA in Hypertension.....	608
12.2. Definition and Etiology	586	15.3.2.3. Impact of Treatment of OSA on BP.....	608
12.3. Diagnostic.....	586	15.3.2.4. Antihypertensive Treatment in Hypertensive Patients with OSA.....	608
12.3.1. BP Measurement Methods	586	15.4. Endocrine Causes	608
12.4. History-Taking	587	15.4.1. Primary Hyperaldosteronism (PH).....	608
12.5. Physical Examination	587	15.4.2. Pheochromocytoma	609
12.7. Ambulatory Blood Pressure Monitoring (ABPM).....	587	15.4.3. Hypothyroidism.....	609
12.8. Therapeutic Aspects.....	587	15.4.4. Hyperthyroidism	609
12.9. Nonpharmacological Therapy.....	587	15.4.5. Primary Hyperparathyroidism.....	609
12.10. Pharmacological Therapy.....	587	15.4.6. Cushing's Syndrome	610
12.11. Follow-up of Children and Adolescents with HT	588	15.4.7. Obesity	610
12.12. Hypertensive Crisis.....	588	15.4.8. Acromegaly.....	610
13. Hypertensive Crisis.....	596	15.5. Pharmacological Causes, Hormones, and Exogenous Substances.....	610
13.1. Definition	596	16. Resistant and Refractory Hypertension	618
		16.1. Definition and Classification.....	618
		16.2. Epidemiology of Resistant Hypertension	618

16.3. Pathophysiology	618
16.4. Diagnostic Investigation	618
16.5. Treatment	618
16.5.1. Nonpharmacological Treatment	618
16.5.2. Pharmacological Treatment	619
16.5.3. New Treatments	619
17. Adherence to Antihypertensive Treatment	622
17.1. Introduction	622
17.2. Concept and Adherence	622
17.3. Treatment Adherence Assessment Methods	622
17.4. Factors Interfering in Adherence to Treatment	623
17.5. Strategies to promote adherence to antihypertensive treatment ..	623
17.6. Conclusion	623
18. Perspectives	625
18.1. Introduction	625
18.2. Definition, Epidemiology, and Primary Prevention	625
18.3. Blood Pressure and Vascular Damage	625
18.4. Cardiac Biomarkers	625
18.5. Diagnosis and Classification	625
18.6. Complementary Assessment and Cardiovascular Risk Stratification ..	626
18.7. Goals and Treatment	626
Reference	628

1. Definition, Epidemiology, and Primary Prevention

1.1. Definition of Hypertension

Hypertension (HT) is a chronic noncommunicable disease (NCD) defined by blood pressure levels for which the benefits of treatment (nonpharmacological and/or pharmacological) outweigh the risks. HT is a multifactorial condition, depending on genetic/epigenetic, environmental, and social factors (Figure 1.1), characterized by persistent high blood pressure (BP), ie, systolic blood pressure (SBP) equal to or greater than 140 mm Hg and diastolic blood pressure (DBP) equal to or greater than 90 mm Hg, measured using the appropriate technique, on at least two different occasions, in the absence of antihypertensive medication. When possible, it is advised that these measurements be validated by assessing BP outside the physician's office using ambulatory blood pressure monitoring (ABPM), home blood pressure monitoring (HBPM), or self-measured blood pressure (SMBP) (see Chapter 3).

1.2. Impact of Hypertension on Cardiovascular Diseases

As an often asymptomatic condition, BP usually progresses to structural and/or functional change to end organs, such as the heart, brain, kidneys, and blood vessels. It is the primary modifiable risk factor, independently, linearly, and continuously associated, for cardiovascular disease (CVD), chronic kidney disease (CKD), and early death. It is associated with metabolic risk factors for cardiocirculatory and renal diseases, such as dyslipidemia, abdominal obesity, glucose intolerance, and diabetes mellitus (DM).¹⁻⁶

In addition, it has a significant impact on socioeconomic and medical costs due to fatal and nonfatal complications to end organs, such as: heart: coronary artery disease (CAD), heart

failure (HF), atrial fibrillation (AF), and sudden death; brain: stroke, ischemic stroke, hemorrhagic stroke, and dementia; kidneys; CKD that may require dialysis therapy; and arterial system: peripheral occlusive atherosclerotic disease (POAD).³⁻⁶

1.3. Risk Factors for Hypertension

1.3.1. Genetics

Genetic factors may influence BP levels from 30 to 50%.⁷ However, due to wide genetic diversity, the gene variants we have studied thus far and Brazilian miscegenation, uniform data for this factor have yet to be identified. Further details about the genetic component of HT can be found in Chapter 3.

1.3.2. Age

SBP becomes a more significant problem with age, the result of the progressive hardening and decreased compliance of the great arteries. Approximately 65 percent of people age 60 or older have HT, and we should take into consideration Brazil's ongoing epidemiological transition, with an even greater number of older adults (age ≥ 60) in the coming decades leading to a substantial increase in the prevalence of HT and its complications.^{7,8}

1.3.3. Sex

Among younger cohorts, BP is higher in men, but rises faster by decade in women. Therefore, in their sixth decades, women's BP is usually higher than men's, as is the prevalence of HT. For both sexes, the frequency of HT rises with age, reaching 61.5% and 68.0% for men and women age 65 or older, respectively.⁷

1.3.4. Race/Ethnicity

Race and ethnicity are important risk factors for HT, but socioeconomic status and lifestyle seem to be more relevant for the differing prevalence of HT than race and ethnicity themselves.^{7,8} The Vigitel 2018 data show that, in Brazil, there was no significant differences between blacks and whites regarding the prevalence of HT (24.9% versus 24.2%).⁹

1.3.5. Overweight/Obesity

There seems to be a direct, continuous, and almost linear relationship between overweight/obesity and BP levels.³⁻⁶ Despite decades of unequivocal evidence that waist circumference (CC) provides both independent and additive information to body mass index (BMI) for predicting morbidity and risk of death, this parameter is not routinely measured in clinical practice. It is recommended that health professionals be trained to properly perform this simple measurement and consider it as an important "vital sign" in clinical practice.³⁻⁶

1.3.6. Sodium and Potassium Intake

High sodium intake has been shown to be a risk factor for high BP and consequently for the greater prevalence of HT. The literature shows that sodium intake is associated with CVD and stroke when mean intake is greater than 2 g of sodium,

equivalent to 5 g of table salt.¹⁰ Sodium excretion studies show that, for those with high sodium intake, SBP was 4,5-6.0 mm Hg higher, and DBP 2,3-2.5 mm Hg higher, than for those at recommended sodium intake levels.¹¹

It should also be stressed that excess sodium intake is one of the main modifiable risk factors for preventing and controlling HT and CVD, and that the Brazilian Unified Health System (SUS) spent USD 102 million in 2013 alone on hospitalizations attributable to excess sodium intake.¹²

Conversely, increased sodium intake reduces blood pressure levels. It is worth highlighting that the effects of potassium supplementation seems to be greater for those with high sodium intake and for black people. Mean salt intake in Brazil is 9.3 g/day (9.63 g/day for men and 9.08 g/day for women), while potassium intake is 2.7 g/day for men and 2.1 g/day for women.^{12,13}

1.3.7. Sedentary lifestyle

There is a direct association between a sedentary lifestyle, high BP, and HT.³⁻⁶ It should be noted that, globally in 2018, the rate of lack of physical activity (less than 150 minutes of physical activity per week or 75 minutes of vigorous physical activity per week) was 27.5%, with greater prevalence among women (31.7%) than men (23.4%).¹⁴

In Brazil, the 2019 Vigitel phone survey found that 44.8% of adults did not perform sufficient levels of physical activity, and rates were worse for women (52.2%) than for men (36,1%).⁹

1.3.8. Alcohol

The impact of alcohol intake has been investigated in various epidemiological studies. There is greater prevalence of HT or high blood pressure levels for those taking six or more doses per day, equivalent to 30 g of alcohol/day = 1 bottle of beer (5% alcohol, 600 mL); = 2 glasses of wine (12% alcohol, 250 mL); = 1 dose (42% alcohol, 60 mL) of distilled beverages (whiskey, vodka, spirits). That threshold should be cut in half for low-weight men and for women.^{15,16}

1.3.9. Socioeconomic Factors

Socioeconomic factors include lower educational levels, inadequate living conditions, and low family income as significant risk factors for HT.^{17,18}

1.3.10. Other Risk Factors for High BP

In addition to the classic factors listed above, it is important to stress that some medications, often acquired without prescription, have the potential to promote high BP or make it harder to control, as do illicit drugs. The subject will be discussed in more detail in Chapter 15. These include monoamine oxidase inhibitors and sympathomimetic, such as decongestants (phenylephrine), tricyclic antidepressants (imipramine and others), thyroid hormones, oral contraceptives, nonsteroidal anti-inflammatory drugs, carbenoxolone and liquorice, glucocorticoids, cyclosporine, erythropoietin, and illicit drugs (cocaine, cannabis, amphetamine and 3,4-methylenedioxymethamphetamine (MDMA)).^{5,19}

1.3.11. Obstructive Sleep Apnea (OSA)

There is clear evidence behind the relation between OSA and HT and increased risk of resistant HT (see also Chapter 15). Mild, moderate, and severe OSA has a dose-response relationship with HT. There is a stronger association for Caucasian and male patients with OSA.^{3-6,20}

1.3.12. Global Epidemiological Data

CVD are the main cause of death, hospitalization, and outpatient medical visits worldwide, including developing countries such as Brazil.²¹ In 2017, complete and revised data from Datasus showed a total of 1 312 663 deaths, 27.3% of which from CVD.²² HT was associated with 45% of cardiac deaths (CAD and HF), 51.0% of deaths from cerebrovascular disease (CVD), and a small percentage of deaths directly related to HT (13.0%). It should be stressed that HT kills more by causing end-organ damage²³ (Figure 1.2).

In 2017, data from Global Burden of Disease (GBD) indicated that CVD accounted for 28.8% of total deaths from noncommunicable diseases (NCD). The GBD study found that there were almost 18 million deaths from CV causes in 2017 (31.8% of total deaths), accounting for 20.6% of total years of life lost (YLL) and 14,7% total DALYs (disability-adjusted life years, ie, years of healthy life lost).^{18,21}

Also according to GBD, SBP increase was found to be the main risk factor, responsible for 10.4 million deaths and 218 million DALYs.²¹ It also accounts for approximately 40.0% of deaths of DM patients, 14.0% of maternal and fetal mortality during pregnancy, and 14.7% of total DALYs from CKD.²⁴⁻²⁶

Globally, in 2010, HT prevalence ($\geq 140/90$ mm Hg and/or use of antihypertensive medication) was 31.0%, higher for men (31.9%) than for women (30.1%).^{17,18}

A study on worldwide trends in blood pressure from 1975 to 2015 assessing 19.1 million adults found that, in 2015, there was an estimated 1.13 billion adults with HT (597 million men and 529 million women), suggesting a 90% increase in the number of people with HT, especially in low- and medium-income countries.^{17,18} The study found that HT prevalence decreased in high-income countries and some medium-income ones, but increased or held steady in lower-income nations. The factors implicated in that increase are likely population aging and greater exposure to other risk factors, such as high sodium and low potassium intake, in addition to sedentary lifestyles.^{17,18}

1.4. Prevalence of Hypertension in Brazil

Countrywide prevalence data tend to vary according to the methodology and sample chosen. According to the 2013 Brazilian National Health Survey, 21.4% (95% CI 20.8-22.0) of Brazilian adults self-report HT, while BP readings and the use of antihypertensive medications indicate that the share of adults with BP at or above 140/90 mm Hg is approximately 32.3% (95% CI 31.7-33.0). HT prevalence was found to be higher among men and, as expected, to increase with age regardless of other parameters, reaching 71.7% for individuals age 70 and older (Table 1.1 and Figure 1.3).²⁷

In 2017, there was a total of 1 312 663 deaths, 27.3% of which from CVD, accounting for 22.6% of all early deaths in Brazil (ages 30 to 69). In one ten-year period (2008 through 2017), it is estimated that 667 184 could be attributed to HT in Brazil.²¹⁻²³

In the death rate per 100 000 inhabitants from 2000 to 2018, we can see a slight uptick in AMI and a jump in direct HT, with 25% and 128% increases, respectively.²³

As for morbidity, we can see the population-adjusted hospitalization trend has been stable over the last ten years (Datusus Hospitalization System) both for all causes and for CVD (Figure 1.3).^{5,23} More of the Brazilian health system's costs can be attributed to HT than to obesity and DM. In 2018, it is estimated that SUS spent USD 523.7 million in hospitalizations, outpatient procedures, and medications.²⁸

Over the last decade, CVD associated with HT account for 77% of the Brazilian Unified Health System's (SUS) hospitalization costs from CAD, and they increased 32% from 2010 to 2019 in Brazilian reais, from R\$ 1.6 billion to R\$ 2.2 billion over the same period.^{28,29}

1.5. Primary Prevention

1.5.1. Introduction

HT is highly prevalent and a major risk factor for CVD and kidney disease, combining genetic, environmental, and social determinants. It is easily diagnosable and effectively treatable by a diverse and highly efficiency therapeutic arsenal with few adverse effects. Even so, globally, the fact that it is an often asymptomatic disease means adherence to care is difficult and it remains mostly uncontrolled worldwide.

That equation makes treatment extremely challenging, and prevention remains the best option from a cost-benefit perspective. An adequate approach to risk factors for HT should be a major point of focus for SUS (the Brazilian Unified Health System). Several aspects of that issue deserve further consideration. Many are interwoven or ad to nonpharmacological treatment (Chart 1.1), detailed in Chapter 8.^{3,5,6,30,31}

1.5.2. Weight Control (LR: I; LEE: A)

Overall and central obesity are associated with increased risk of HT. On the other hand, weight loss promoted lower BP both for normotensive and for hypertensive individuals.^{3,5,6} Being "as lean as possible" within the normal BMI range may be the best suggestion for primary prevention of HT.^{3,5,6, 32-36}

1.5.3. Healthy Diet (LR: I; LE: A)

Several diets have been proposed for HT prevention which also favor hypertension control and contribute to health as a whole.^{5,37} One major proposal to that end is the DASH diet and its variants (low fat, Mediterranean, vegetarian/vegan, Nordic, low carbohydrate content, etc.). The benefits are even greater when combined with lower sodium intake.^{5,37-40}

Every report on the subject recommends eating healthy amounts of fruits, greens, vegetables, cereal, milk, and dairy

products, as well as lowering salt and fat intake.³⁷⁻⁴¹ A meta-analysis compared varieties of these diets with the standard diet and found a greater decrease in SBP (-9.73 to -2.32 mm Hg) and DBP (-4.85 to -1.27 mm Hg) in the proper diet group.³⁹ Socioeconomic and cultural aspects have to be taken into account to ensure adherence to a given kind of dietary recommendation.^{3,5,6,37}

1.5.4. Sodium (LR: I; LE: A)

Excess sodium intake is one of the main modifiable risk factors for preventing and controlling HT and CVD.²⁹ Sodium restriction has been shown to lower BP in several studies. A meta-analysis found that a 1.75 g decrease in daily sodium intake (4.4 g of salt/day) is associated with a mean decrease of 4.2 and 2.1 mm Hg in SBP and DBP, respectively. The BP decrease from sodium restriction is greater in blacks, older adults, diabetic patients, and individuals suffering from metabolic syndrome (MS) and CKD.³⁷

In the general population, individuals are recommended to restrict their sodium intake to approximately 2 g/day (equivalent to about 5 g of salt per day).³⁻⁶ Effectively lowering salt intake is not easy, and low-salt foods are often underappreciated. Patients should be advised to take care with how much salt they add to their food and not to eat high-salt items (industrialized and processed foods).³⁻⁶

Decreasing Brazilian salt intake remains a high public health priority, but requires combined efforts from the food industry, all levels of government, and the public in general, since 80% of salt comes from processed foods.^{3-6,10,12,40} Adequate intake of fruits and vegetables leverages the beneficial effects of a low-sodium diet on BP. Salt substitutes with potassium chloride and less sodium chloride (30 to 50%) are useful to help lower sodium intake and increase potassium intake, despite their restrictions.⁴²

1.5.5. Potassium (LR: I; LE: A)

The relationship between potassium supplementation and lowering HT is relatively well understood.⁴³ Potassium supplementation represents a safe alternative, with no major adverse effects and modest but significant impact on BP, and can be recommended to help prevent the onset of HT.⁴³⁻⁴⁷ Adequate potassium intake, on the order of 90 to 120 mEq/day, may lead to a 5.3 mm Hg decrease in SBP and a 3.1 mm Hg decrease in DBP.⁴⁵ Its intake can increase by opting for sodium-poor and potassium-rich foods, such as beans, peas, dark leafy greens, bananas, melons, carrots, beets, dried fruit, tomatoes, potatoes, and oranges.³

1.5.6. Physical Activity (LR: I; LE: A)

A sedentary lifestyle is one of the ten most important risk factors for global mortality, causing approximately 3.2 million deaths per year.^{48,49}

A meta-analysis of 93 papers and 5223 individuals showed that aerobic, dynamic resistance and isometric resistance training lower SBP and DBP at rest by 3.5/2.5, 1.8/3.2 and 10.9/6.2 mm Hg, respectively, in the general population.⁵⁰⁻⁵²

All adults should be advised to practice at least 150 min/week of moderate physical activity or 75 min/week of vigorous activity. Aerobic exercises (walking, running, bicycling, or swimming) may be practiced for 30 minutes 5 to 7 times per week. Resistance training two to three days per week is also recommended.^{50,52} For additional benefits, in healthy adults, a gradual increase in physical activity to 300 minutes per week of moderate-intensity physical activity or 150 minutes per week of vigorous physical activity, or an equivalent combination of the two, ideally with supervised daily physical exercise.⁵⁵

1.5.7. Alcohol (LR: IIA; LE: B)

Alcohol consumption is estimated to account for approximately 10 to 30% of HT cases and approximately 6% of all-cause mortality worldwide.^{3-6,15,56-59} Among drinkers, intake should not exceed 30 g of alcohol/day, ie, 1 bottle of beer (5% alcohol, 600 mL), two glasses of wine (12% alcohol, 250 mL), or one 1 dose (42% alcohol, 60 mL) of distilled beverages (whiskey, vodka, spirits). That threshold should be cut in half for low-weight men, women, the overweight, and/or those with high triglycerides. Teetotalers should not be encouraged to drink.^{3-6,15}

1.5.8. Psychosocial Factors (LR: IIb; LE: B)

There is a wide variety of techniques used to control emotional stress and contribute to HT prevention, but there is still a dearth of robust studies on the subject.^{3-6,60} Practicing emotional stress control can help CV reactivity, BP itself, and BP variability.⁶¹⁻⁶³

1.5.9. Dietary Supplements (LR: I to III; LE: A and B)

The effects of dietary supplements on lowering BP are usually small and heterogeneous.⁵⁸⁻⁶⁸ There is evidence that the following supplements can help lower BP to a small degree: vitamin C, food-derived bioactive peptides, garlic, dietary fiber, flaxseed, dark chocolate (cocoa), soy, organic nitrates, and Omega-3 fatty acids.^{38,47,69} Magnesium supplements, multivitamins, tea, and coenzyme Q10 have not been shown to lead to significant decreases in BP.^{64,65,70}

1.5.10. Smoking (LR: I; LE: A)

Regardless of its impact on BP, tackling this issue is critical, since smoking is the only completely avoidable risk factor for cardiovascular disease and death, and fighting it is paramount.^{3-6,71-75} From a prevention standpoint, the WHO recommends the following strategies for tobacco control: prevent the young from trying cigarettes, since the

odds of becoming addicted for those who try are over 50%; and enforce the country's tobacco legislation, particularly the prohibition of marketing tobacco products to minors, in addition to other activities directed at this age group.⁷² Chemical and psychological addiction makes the fight against smoking hard, but the benefits of cessation for CV mortality are apparent in the short run.^{71,73-75}

Rigor in fighting and controlling tobacco use, continuous guidance and unconditional psycho-emotional support for smokers, and occasionally prescribing medication have been shown to be the most effective approach.⁷³ It is also important to protect individuals against exposure to secondhand smoking, which also implies greater risk.⁷⁴

1.5.11. Spirituality (LR: I; LE: B)

There is growing evidence that spirituality (S), a concept transcending religiosity (R), signifying a set of moral, emotional, behavioral, and attitudinal values toward the world, provides benefits in terms of CV risk, mortality, and, in particular, blood pressure control.⁷⁶

The Black Women's Health Study showed that women who coped with stressful situations through spirituality and religiosity had lower risk of developing HT over a 10-year follow-up period (incidence ratio = 0.87; 95% CI 0.75-1.00), and the association was stronger for those reporting higher levels of stress. The survey also found that R/S situations helped modulate and smooth out the challenges of daily life and brought benefits in terms of BP control.⁷⁷

1.6. Strategies for the Implementation of Preventive Measures

Lifestyle changes (LSCs) are hard to implement, and society as a whole should work together to support that effort. It is important to establish and support ongoing health education programs directed at K-12 and vocational school students, staff, corporations, and the community. Using the media to raise awareness is an important strategy; periodic focused campaigns (City, State and/or National Hypertension and Prevention Day—Federal Law 10.439 from April 30, 2002, HT Week, the International Society of Hypertension's May Measurement Month, etc.); and additional actions: incorporating HT prevention, detection, and control to primary health care programs, including children and adolescents, and particularly in school health programs; deploying multidisciplinary care programs; strengthening government norms to lower the saturated fat and sodium content of industrialized foods; enhancing nutrition fact labels; and using efficient health indicators to monitor HT prevention and control actions and their results.³⁻⁶

Key Takeaways

The numbers defining hypertension are arbitrary, but represent values for which the benefits of treatment (nonpharmacological and/or pharmacological) outweigh the risks.

HT is a multifactorial condition (genetics, environment, life habits and socioeconomic factors).

HT is a major risk factor for cardiovascular and kidney diseases.

HT is highly prevalent, easily diagnosed and can be properly treated, but low adherence means it is hard to control.

HT prevention is cost-effective and also the best way to decrease cardiovascular morbidity and mortality.

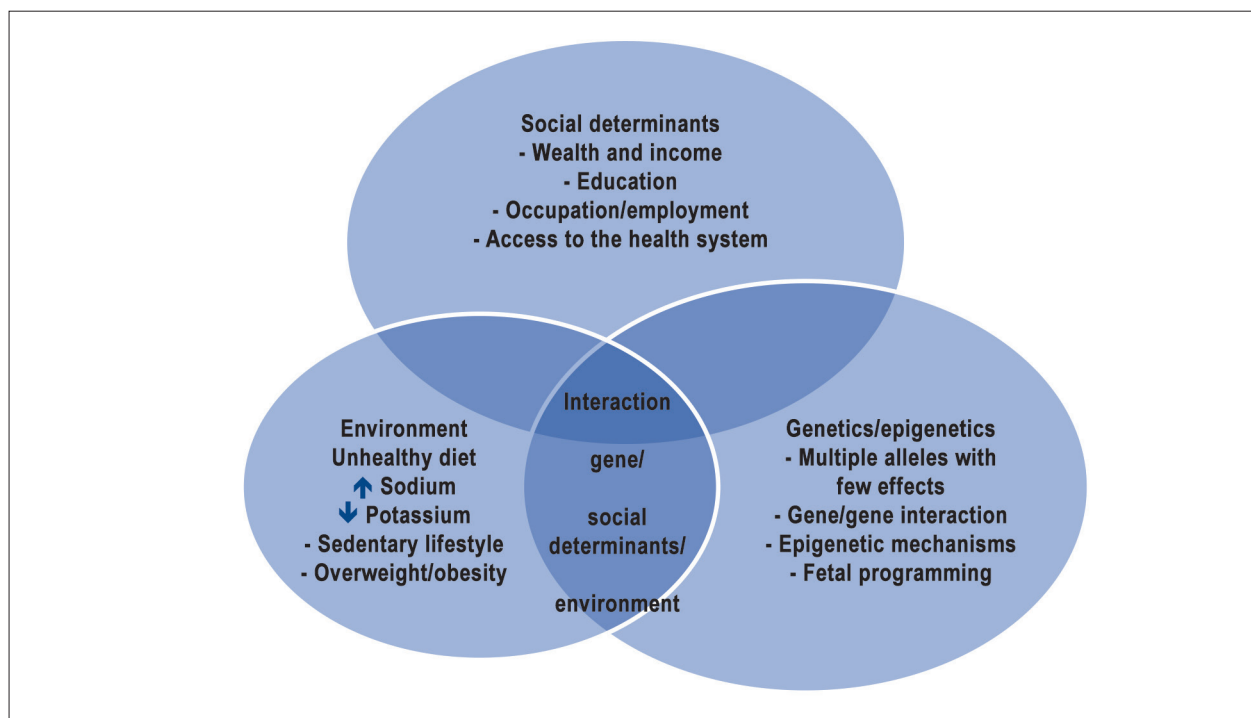


Figure 1.1 – Schematic description of major determinants of blood pressure and hypertension and their interactions in adults. Genetic/epigenetic, environmental, and social determinants interact to increase the BP of hypertensive patients and in the general population. ↑increased; ↓decreased.

Source: Carey et al. 2008.⁶

Table 1.1 – Prevalence of hypertension and 95% confidence interval according to three criteria

	Self-reported HT (Vigitel)	Measured BP ≥ 140/90 mm Hg (PNS, 2013)	Measured BP ≥ 140/90 mm Hg and/or use of antihypertensive medication (PNS, 2013)
Total	21.4% (20.8-22.0)	22.8% (22.1-23.4)	32.3% (31.7-33.0)
Male	18.3 (17.5-19.1)	25.8 (24.8-26.7)	33.0 (32.1-34.0)
Female	24.2 (23.4-24.9)	20.0 (19.3-20.8)	31.7 (30.9-32.5)

HT: hypertension; BP: blood pressure. Source: Nilson et al. 2020.²⁹

Guidelines

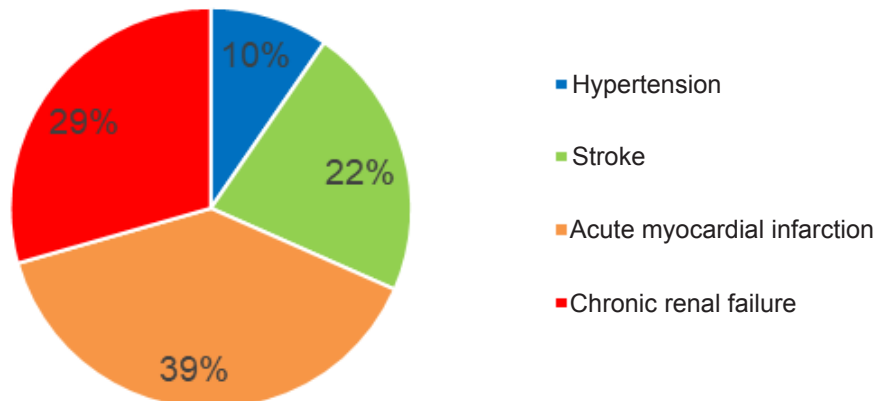


Figure 1.2 – Percentage of deaths from hypertension, acute myocardial infarction, stroke, and chronic renal failure (Brazil, 2000).

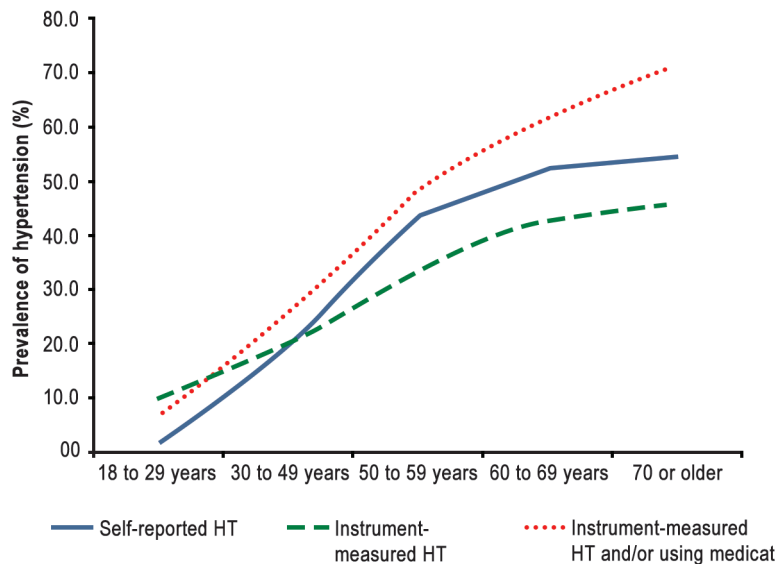


Figure 1.3 – Population prevalence of hypertension according to various diagnostic criteria, in adults 18 or older, both genders, by age group (Brazil, 2013).
Source: Nilson et al., 2020.²⁹

Chart 1.1 – Main interventions that prevent hypertension

Modality	NP Intervention	Dose	Difference in SBP measured
Weight control	Body weight/fat	Reach ideal weight. Expected decrease of 1mm Hg per kg of body weight lost	- 2/3 mm Hg
Healthy diet	DASH diet	Diet rich in fruits, vegetables, grain, and low fat content Reduction in saturated and trans fats	- 3 mm Hg
Lower sodium intake	Sodium intake	Ideal < 2 g or at least 1.0 g/day less	- 2/3 mm Hg
Increased potassium intake	Potassium intake	3.5 to 5.0 g/day in a potassium-rich diet	- 2 mm Hg
Physical activity	Aerobic	150 min/week	- 5/7 mmHg
	Dynamic resistance	8 to 10 exercises for the major muscle groups, 1 to 3 sets, 50 to 80% of 1 RM	
	Isometric resistance	Unilateral handgrip exercise or 1 leg, 4 sets, 2 min isometric contraction, 30% of maximum voluntary contraction (MVC), 2-3 min break between sets	- 4/5 mm Hg
Alcohol intake	Alcohol consumption	For alcohol drinkers Men ≤ 2 drinks Women ≤ 1 drink	- 4/5 mm Hg

mm Hg: millimeters of mercury; NP: nonpharmacological; RM: repetition maximum; SBP: systolic blood pressure. Source: Adapted from Carey et al., 2018.⁶

2. Blood Pressure and Vascular Damage

2.1. Introduction

High blood pressure (BP) values are traditionally associated with risk for ischemic heart disease, stroke, chronic kidney disease (CKD), and early death. A classic meta-analysis of 61 prospective studies, tracking 12.7 million persons-year and a record of 56 000 deaths from coronary artery disease (CAD) or stroke, produced solid observational evidence.⁷⁸ That meta-analysis showed that the risk begins with BP values as low as 115 mm Hg for systolic BP (SBP) or 75 mm Hg for diastolic BP (DBP), doubling for every 20 mm Hg increase in SBP or 10 mm Hg increase in DBP. Despite observational evidence, these findings have not been integrated with the definition of hypertension (HT) diagnosis, which has remained at 140/90 mm Hg for many years.

Thus, patients are still classified as hypertensive with BP levels above 140/90 mm Hg, and individuals with SBP from 120 to 139 mm Hg and DBP from 80 to 89 mm Hg are classified as having normal BP or as prehypertensives, but these have higher cardiovascular risk in comparison with their peers with normal or optimum BP levels. The impact of prehypertension (systolic BP 130–139 mm Hg, diastolic BP 85–89 mm Hg) on vascular risk was described in 2001 by Vasan et al.,⁷⁹ who analyzed 6859 participants in the Framingham Heart Study. In that study, the authors found an increase in absolute risk for cardiovascular (CV) events. Several other studies have since been published, and their analysis included lower risk patients (systolic BP 120–139, diastolic BP 80–89 mm Hg), such as the Hisayama study, by Fukuhara et al.,⁸⁰ which also found increased risk for CV disease.

Several other studies have been published since the early work by Vasan et al., which has led to a meta-analysis by Han et al.⁸¹ in 2019, which analyzed 47 studies and a total population of 491 666 individuals. In that meta-analysis, after controlling for multiple CV risk factors, prehypertension increased the total risk of disease by 40%, including that 12.09% of CV disease, 13.26% of coronary diseases, 24.60% of myocardial infarctions (MIs), and 19.15% of strokes could have been prevented if prehypertension was effectively controlled.

That leads to the conclusion that prehypertensive individuals, even if not considered actually hypertensives, should be better assessed and stratified. Noninvasive complementary examinations can evaluate the impact of BP on vessels and analyze early vascular damage both in hypertensive and prehypertensive patients,⁸² such as flow-mediated dilation (FMD), which checks endothelial function, and pulse wave velocity (PWV) and ankle-brachial index (ABI), which check the medial layer. The goal of this chapter is to show the impact of increased BP on CV risk, on endothelial dysfunction (damage to the vascular endothelial layer) and arterial stiffness (damage to the vascular medial layer) before HT is diagnosed.

2.2. Blood Pressure, Clinical Outcomes, and Cardiovascular Damage

In the meta-analysis by Law et al.,⁸³ lowering SBP by 10 mm Hg in randomized controlled trials led to AMI and stroke prevention at the same rate estimated by observational studies

for the same BP increase. The same was true for a more recent meta-analysis.⁸⁴ In this study, the relative risk reduction for CV events in trials where participants were treated to achieve SBP targets from 120 to 124 mm Hg, compared to over 160 mm Hg, was 64%, close to the 75% risk reduction for an estimated 40 mm Hg decrease in SBP from the Prospective Studies Collaboration meta-analysis.⁷⁸ Other meta-analyses have converged for these findings, and the largest included 600 000 participants from clinical trials.⁸⁵ The SPRINT clinical trial added more evidence to the studies discussed above.⁸⁶ The incidence of CVD decreased by 25% in patients randomized for a SBP < 120 mm Hg (intensive treatment), compared to those randomized for a target BP level below 140 mm Hg. There was a 43% decrease in CVD mortality and a 27% decrease in all-cause mortality. A similar benefit was found for participants 75 or older over the baseline, including frail individuals⁸⁷ (LR: 1 LE: A).

More recently, several cohort studies with large sample sizes have come out showing that increased BP creates similar risks for other CV outcomes as those found for CAD and stroke. These include heart failure (HF), with and without preserved ejection fraction (EF),⁸⁸ atrial fibrillation,⁸⁹ valvular heart disease,^{90,91} peripheral arterial disease,⁹² chronic kidney disease (CKD),^{93,94} dementia,^{95,96} and Alzheimer's disease.⁹⁷ Diabetes mellitus,⁹⁸ erectile dysfunction,⁹⁹ and age-related macular degeneration¹⁰⁰ are likely consequences of sustained high BP. In general, these consequences are externalized after many years of exposure to high blood pressure levels, usually to values previously not associated with CV risk.¹⁰¹ The consequences of high BP can be classified by onset as early or late and comprise most CVD (Chart 2.1). Recently, authors have theorized that CVD is predominantly caused by the rightward shift of the BP distribution curve on a global scale.¹⁰²

There is little experimental evidence showing the long-term prevention of high BP. Running clinical trials to show the effectiveness of interventions in the early stages of high BP and, consequently, in decreasing outcomes is a major challenge, since it would require long intervention periods. Despite this limitation, the SPRINT-Mind trials showed that the strategy of lowering SBP to below 120 mm Hg was associated with the decreased incidence of mild cognitive impairment and dementia¹⁰³ as well as Alzheimer's markers in magnetic resonance imaging.¹⁰⁴

In addition to increased risk of clinical outcomes from high BP, there was also evidence of preclinical vascular and cardiac damage from BP readings lower than those traditionally used to diagnose HT. Cardiac consequences have also been found from mildly elevated blood pressure levels, categorized as prehypertension.^{105,106} The PREVER trial found that, in these cases, lowering BP leads to smaller ECG-estimated ventricular mass,¹⁰⁷ as well as an almost 50% decrease in HT.

Risk estimates for increased incidence for the diseases listed in Chart 2.1 have increased significantly in recent years as lower BP values were included in mathematical models. The most conservative attribute 49% of infarctions and 62% of strokes to BP above 115/75 mm Hg.¹⁰⁸

Many justifications have been offered to explain centenarians' life spans. Curiously, even reports that found

late onset of HT and CV events for these individuals¹⁰⁹ did not attribute a causal relationship between those conditions. Considering the discussion above, it is natural to conclude that vascular aging is not inexorable.¹⁰² Therefore, it can be deduced that the key for very long life spans probably consists of maintaining BP at actually normal values. More recently, the 14-year follow-up of participants in the MESA (Multi-Ethnic Study of Atherosclerosis) study¹¹⁰ with no other CV risk factors found that SBP above 100 mmHg increased the risk of CV events threefold compared to participants with SBP between 90 and 99 mm Hg.

The evidence available allow us to hypothesize that, in the future, reference values for a HT diagnosis, as well as therapeutic targets, may be changed and brought closer to levels we now consider normal or optimum BP. More solid and robust evidence is still needed before that change can occur, however.

2.3. Blood Pressure, Inflammation, and Endothelial Dysfunction

HT and its complications are mediated by various mechanisms sharing one common trait, ie, endothelial dysfunction, characterized by the low availability of nitric oxide (NO) and the consequent local imbalance between arteriole relaxing and contracting factors.¹¹¹ Endothelial dysfunction is a consequence of the imbalance between endothelial NO synthase (eNOS) or the transformation of NO into the free radical peroxynitrite (NOO⁻).¹¹² In that case, vasodilation mediated by several peptides, including bradykinin and angiotensin 1-7, is impaired, leading to increased peripheral vascular resistance and alterations in endothelial permeability. The onset of a chronic inflammatory state in HT patients via the increased production of proinflammatory cytokines (eg, leukocyte adhesion molecules such as endothelin-1 and angiotensin II) decreases eNOS expression,¹¹³⁻¹¹⁵ while increased oxidative stress accelerates NO degradation. Reduced local NO availability increases smooth vascular muscle tone, induces smooth muscle cell proliferation in the medial layer, and increases endothelial permeability, facilitating the passage of low-density lipoprotein (LDL-C) into the subendothelial space, which seems to be the initial event behind the onset of atherosclerosis. Thus, endothelial dysfunction would be at the root of two chronic diseases that usually go together, ie, HT and atherosclerosis. Therefore, identifying the degree of endothelial dysfunction might be an important step in assessing the clinical course of HT. At the biochemical level, ultrasensitive C-reactive protein (CRP) seems to be the most adequate clinically available marker to assess endothelial dysfunction.

Currently, the most widely used technique for analyzing endothelial function in vivo in clinical settings is brachial artery FMD,¹¹⁶⁻¹¹⁹ a noninvasive ultrasound method correlated with coronary endothelial function^{120,121} and an independent predictor of CV disease.^{121,123} However, its availability is limited. Endothelium-dependent dilation is a consequence of brachial artery relaxation in response to increased shear stress and local release of NO.¹¹⁹ The association between FMD and CV prognosis is that it reflects the bioavailability of NO.¹²⁴ FMD may improve the predictive power of risk calculations based

on traditional risk factors, including for young hypertensive patients.^{119,123} Antihypertensive medications that increase the bioavailability of NO and statins may be an interesting option for clinical management^{5,37,125} in order to maintain or preserve endothelial function for both asymptomatic patients and those with established CAD.

2.4. Blood Pressure and Arterial Stiffness

Assessments of vascular damage, a common finding in HT, are increasingly part of clinical practice. The damage involves microvascular alterations, atherosclerosis, increased arterial stiffness, and endothelial dysfunction.¹²⁶ There is probably a genetic component to arterial stiffness,¹²⁷ but there are also two other important determinants: age and BP levels.¹²⁸

Age has greater impact on proximal (central) arteries, predominantly elastic, than on peripheral arteries, predominantly muscular. Central arteries grow stiffer with age, while muscular arteries change less. With age comes elastin fragmentation and generation and progressive accumulation of collagen, accompanied by calcium deposits in the medial layer of arteries, and consequently increased arterial stiffness.^{128,129}

Sustained BP increases trigger the onset of arterial medial hypertrophy, as it causes quantitative and qualitative alterations in the components of the arterial walls (elastin, collagen, and smooth muscle cells), leading to mechanical adaptations.^{127,128,130} These findings have been described both for animal models¹³¹ and for in vitro studies and ex vivo organ cultures,^{132,133} where mechanosensitive cells respond to increased stress with extracellular matrix production. Therefore, HT accelerates vascular aging, a local mechanobiological response to increased induced stress from higher BP and, consequently, greater arterial stiffness (stiffness as a consequence).^{128,134}

However, several studies have found increased carotid or aortic stiffness in normotensive individuals, despite normal BP levels.¹³⁵⁻¹³⁸ Stiffer arteries create higher impedance for ventricular ejection, requiring higher blood pressure to keep blood flow constant. Thus, increased arterial stiffness may also lead to increased BP in the long run and, consequently, to CV risk. Studies have shown that arterial stiffness may precede HT, theorizing stiffness as a cause. Humphey et al. (2016)¹³⁴ described the mechanism as neither cause nor consequence alone, but rather as both, ie, a positive feedback loop where stiffness leads to HT and HT leads to stiffness.

The impact of HT on the medial layer of arteries may be assessed using biomarkers capable of detecting damage and various levels of impairment, determining impact on mortality, predicting CV events, adding information to known risk factors, sufficiently stratifying risk to change therapeutic recommendations, and adding information to justify additional costs.¹³⁹ Biomarkers available for assessing arterial stiffness can be found in the following subsections.

2.4.1. Ankle-Brachial Index (ABI)

ABI is the ratio between systolic pressure in the ankle and the arm,¹⁴⁰ considered a marker for arterial stiffness in patients without peripheral arterial disease.¹⁴¹ It may be measured

using Doppler ultrasound or simply applying the oscillometric method, cheaper and more easily available, and readings obtained using both techniques are strongly correlated.¹⁴² According to a 2008 meta-analysis,¹⁴³ $ABI \leq 0.90$ is associated with approximately twice the 10-year age-adjusted mortality, CV mortality, and higher rate of coronary events. Using ABI has led to the reclassification of CV risk categories and changing therapies for 19% of men and 36% of women.¹⁴³ ABI as a predictor of cardiovascular risk is LR: IIa, LE: B.

2.4.2. Pulse Wave Velocity (PWV)

PWV is considered the gold standard for arterial stiffness assessments due both to how easy it is to obtain and to the large body of evidence showing its association with CV disease regardless of traditional risk factors.^{144,145}

Carotid-femoral PWV (cfPWV) is determined by dividing traveled distance by travel time ($cfPWV = \text{distance}/\text{time}$). The time may be measured directly in the same pulse wave or indirectly using an electrocardiogram. This noninvasive, robust and validated measure was standardized in an expert consensus document published by a European group in 2012.¹⁴⁶

Currently available validated methods include pulse tonometry^{147,148} and piezoelectric^{149,150} and oscillometric mechanotransducers.^{151,152} In 2015, the American Heart Association published a position paper on standardizing the use of these devices to assess arterial stiffness.⁸²

Increased arterial stiffness is predictive of outcomes. This was shown for cfPWV in hypertensive patients in the early 2000s^{153,154} and confirmed in several studies and two subsequent meta-analyses.^{155,156} The first meta-analysis, from 2010,¹⁵⁵ included 15877 patients from 17 trials, and showed that, risk-adjusted for age, sex, and risk factors, a 1 m/s increase in PWV led to a 14% increase in CV events, 15% in CV mortality, and 15% in all-cause mortality. In addition, a one standard deviation increase was associated to increases of 47%, 47%, and 42%, respectively. The second meta-analysis, published in 2014,¹⁵⁶ featuring 17635 patients from 16 trials, found that, for every one standard deviation increase in PWV, the risk increased 35% for CAD, 54% for stroke, and 45% for CVD.

As well as predicting outcomes, adding PWV to traditional CV risk factors helps with stratification. The first study to show

improved risk stratification from adding PWV to other CV risk factors was performed on a population sample from the Framingham cohort.¹⁵⁷ Later, the meta-analysis by Ben-Shlomo et al. (2014)¹⁵⁶ showed a 13% increase in risk prediction for individuals at intermediate risk when PWV was added.

Though PWV is relevant for event prediction and risk stratification, it is still little used in clinical practice. In 2019, a European group published a score¹⁵⁸ based on clinical variables to prioritize individuals for PWV assessments. The score assesses easily available clinical variables and is known by the acronym SAGE: S (*systolic blood pressure*), A (*age*), G (*fasting plasma glucose*), and E (*estimated glomerular filtration rate*). PWV increases can be predicted accurately from that score. Therefore, we can prioritize arterial stiffness assessments for select hypertensive patients, improving its deployment in clinical practice.

The cutoff value for normal PWV, in most studies and guidelines, is under 10 m/s. However, due to the influence of age on arterial stiffness, current proposed reference values take into account the various age ranges and sex, as established by the European group in 2010¹⁴⁴ using tonometry, and more recently in a Brazilian study using oscillometric devices (Table 2.1).¹⁵⁹ PWV as a predictor of cardiovascular risk is LR: IIa, LE: A.

2.4.3. Central Blood Pressure

Central (aortic, carotid) blood pressure does not correspond to peripheral (brachial) blood pressure due to pulse amplification from the aorta to the periphery; the former is more relevant for CV pathogenesis than the latter.¹⁶⁰ Currently, central blood pressure can be easily measured by noninvasive methods using the same equipment utilized and validated for measuring PWV.^{151,161,162}

Central hemodynamic indices are independent predictors of future CV events and all-cause mortality according to the meta-analysis by Vlachoupoulos et al., which included 11 studies and a total of 5648 individuals with a mean follow-up period of 45 months.¹⁶⁰ Central blood pressure reference values were established by the European group in 2014 using tonometry,¹⁶³ and more recently in a Brazilian study with oscillometric devices (Table 2.1).¹⁵⁹ Central blood pressure as a predictor of cardiovascular risk is LR: IIa LE: B.

	Level of recommendation	Level of evidence
Blood pressure above 120 mm Hg increases vascular damage and cardiovascular risk	I	A
Use of serum markers to identify endothelial dysfunction	IIb	B
Use of brachial artery FMD (the gold standard technique for in vivo endothelial function analysis) in identification of endothelial dysfunction	IIb	B
Use of FMD for cardiovascular risk stratification	IIb	B
Arterial stiffness assessed with PWV is an independent predictor of cardiovascular risk, and its assessment, when possible, may make the risk stratification more accurate	IIa	A
ABI is an independent predictor of cardiovascular risk	IIa	B
Central blood pressure is an independent predictor of cardiovascular risk	IIa	B

Key Takeaways

Prehypertension increases cardiovascular risk.

Vascular damage is not found only in the hypertensive and may also be found in prehypertensives.

There are noninvasive tests to assess early vascular damage, but they are not always available.

Arterial stiffness analysis with PWV is an independent predictor of cardiovascular risk, and it may be assessed in clinical practice, when available.

Other methods, such as ABI and central blood pressure, may also be used to assess cardiovascular risk. FMD is more widely used in research settings.

Chart 2.1 – Early and late-onset consequences of chronic high BP²⁵

Early- and late-onset diseases

Stroke
Coronary heart disease
Heart failure
Cardiovascular death

Late-onset disease

Hypertensive cardiomyopathy
Heart failure with preserved ejection fraction
Atrial fibrillation
Valvular heart disease
Aortic syndromes
Peripheral arterial disease
Chronic kidney disease
Dementia
Diabetes mellitus
Erectile Dysfunction

Guidelines

Table 2.1 – Reference values for central systolic pressure and pulse wave velocity in Brazilian and European populations with and without cardiovascular risk factors^{69,84,85}

	Normal population — no cardiovascular risk factors				Population with cardiovascular risk factors			
	Brazilian ¹		European ²		Brazilian ¹		European ²	
	Women	Men	Women	Men	Women	Men	Women	Men
CBP								
< 30 years	101 (90-93-113-119)	113 (90-93-113-119)	95 (80-88-102-110)	103 (92-97-109-115)	118 (102-109-127-131)	123 (107-114-132-144)	101 (88-94-110-124)	110 (95-102-120-130)
30-39 years old	109 (96-102-117-123)	114 (96-102-117-123)	98 (84-90-108-119)	103 (88-05-112-120)	120 (102-110-130-143)	125 (108-116-133-141)	111 (92-100-127-141)	114 (95-103-129-144)
40-49 years old	110 (99-103-117-122)	116 (99-103-117-122)	102 (87-93-113-123)	106 (90-97-114-123)	121 (104-110-134-146)	123 (108-115-131-141)	116 (95-104-133-146)	118 (97-106-132-144)
50-59 years old	110 (97-104-120-124)	112 (97-104-120-124)	110 (93-100-119-127)	110 (96-102-118-126)	124 (106-114-135-146)	124 (105-114-134-144)	120 (100-109-134-148)	123 (102-111-137-150)
60-69 years old	114 (100-103-121-126)	112 (100-105-120-125)	114 (97-105-122-129)	114 (97-105-122-128)	127 (105-115-141-154)	123 (103-112-136-149)	128 (105-115-141-154)	128 (105-115-142-155)
≥ 70 years	113 (100-103-121-126)	116 (100-103-121-126)	118 (100-109-126-131)	116 (99-107-124-130)	131 (108-118-146-165)	125 (102-111-140-156)	138 (113-126-152-164)	135 (113-124-147-160)
	Normal population — no cardiovascular risk factors				Population with cardiovascular risk factors			
	Brazilian ¹		European ³		Brazilian ¹		European ³	
	Women	Men	Women	Men	High normal	Stage I HT	Stage II HT	
< 30 years	4.9 (4.4-4.5-5.0-5.3)	5.2 (4.9-5.1-5.4-5.7)	6.1 (5.3-7.1)	5.3 (4.7-5.0-5.6-6.0)	5.3 (5.0-5.3-5.8-6.3)	6.7 (5.8-7.9)	7.2 (5.7-9.3)	7.6 (5.9-9.9)
30-39 years old	5.4 (5.0-5.2-5.8-6.1)	5.7 (5.3-5.5-5.9-6.1)	6.4 (5.2-8.0)	5.8 (5.3-5.5-6.2-6.7)	6.1 (5.5-5.8-6.4-6.7)	7.0 (5.5-8.8)	7.2 (5.5-9.3)	7.6 (5.8-11.2)
40-49 years old	6.4 (5.7-6.0-6.7-6.9)	6.5 (5.9-6.2-6.8-7.0)	6.9 (5.9-8.6)	6.8 (6.0-6.4-7.2-7.7)	6.8 (6.2-6.4-7.1-7.5)	7.7 (6.5-9.5)	8.1 (6.8-10.8)	9.2 (7.1-13.2)
50-59 years old	7.5 (6.7-7.0-7.8-8.2)	7.4 (6.9-7.2-7.9-8.0)	8.1 (6.3-10.0)	7.9 (7.1-7.5-8.3-8.8)	7.9 (7.1-7.5-8.3-8.7)	8.4 (7.0-11.3)	9.2 (7.2-12.5)	9.7 (7.4-14.9)
60-69 years old	8.9 (8.1-8.5-9.2-9.4)	8.9 (8.2-8.6-9.1-9.6)	9.7 (7.9-13.1)	9.3 (8.4-8.8-9.8-10.4)	9.2 (8.4-8.7-9.7-10.2)	9.8 (7.9-13.2)	10.7 (8.4-14.1)	12.0 (8.5-16.5)
≥ 70 years	11.3 (10.2-10.4-12.5-13.2)	11.0 (10.1-10.6-11.6-12.3)	10.6 (8.0-14.6)	11.8 (10.2-10.8-12.9-14.0)	11.2 (9.9-10.4-12.1-13.2)	11.2 (8.6-15.8)	12.7 (9.3-16.7)	13.5 (10.3-18.2)

¹ Brazilian reference values (oscillometry), ² European CBP reference values, median (10th, 25th, 75, 90th percentiles), ³ European PWV reference values (tonometry), median (10th, 90th percentiles). European reference values for PWV are not divided by sex. CBP: central blood pressure; PWV: pulse wave velocity.

3. Diagnosis and Classification

3.1. Introduction

The initial assessment of a patient with hypertension (HT) comprises diagnostic confirmation, suspicion, and identification of the secondary cause, and assessment of cardiovascular (CV) risks. End-organ damage (EOD) and associated diseases should also be investigated. The assessment comprises blood pressure (BP) measurement in and/or out of the office, using proper techniques and validated and well calibrated equipment, taking the patient's medical history (personal and family), physical examination, and clinical and laboratory investigation. All hypertensive patients should undergo general assessments, in addition to complementary assessments for specific groups.¹⁶⁴

3.2. Blood Pressure Measurement at the Physician's Office

All medical assessments should include blood pressure measurements, whatever their specialty, and all other health care professionals should be properly trained in the process. Diagnosing HT and its phenotypes, as well as the management of the diagnosis, is the exclusive province of physicians.

Auscultatory or oscillometric sphygmomanometers are the preferred instruments for BP measurement. These devices should be validated according to standardized protocols and conditions,¹⁶⁵ and their calibration checked annually (for oscillometric devices) or every six months (for auscultatory devices), or following Inmetro/Ipem recommendations.¹⁶⁶ Initially, BP should be measured in both arms, preferably by simultaneous double arm measurement. If the difference between arms is > 15 mm Hg for SBP, there is increased CV risk,¹⁶⁷ which may be connected to atheromatous vascular disease. All subsequent measurements should be performed on the arm with the highest BP values. If HT secondary to coarctation of the aorta is suspected, blood pressure should also be measured in the lower limbs, using properly sized cuffs for arm or thigh circumference (Chart 3.1).¹⁶⁴

In older adults, diabetic patients, dysautonomia patients, or individuals taking antihypertensive medications, BP should also be measured 1 minute and 3 minutes after standing up (motionless).¹⁶⁸ Orthostatic hypotension is defined as a SBP decrease ≥ 20 mm Hg or a DBP decrease ≥ 10 mm Hg within the 3rd minute standing up and is associated with higher risk of mortality and cardiovascular events.¹⁶⁹

Charts 3.2 and 3.3 summarize the procedures and steps recommended for proper BP measurement. It should be stressed that improper BP measurements may lead to inaccurate classification, overestimating or underestimating the patient's true BP, and consequently to unnecessary treatment or lack of treatment for misassessed hypertensive patients. Given the simplicity of measuring BP by oscillometry, using a brachial oscillometric device may be preferable to auscultation when both techniques are available.¹⁷⁰ The differences between both techniques for measuring BP are highlighted in Chart 3.3.

In the *Systolic Blood Pressure Intervention Trial* (SPRINT),⁸⁶ a new mode of measuring BP at the physician's office without an attending health care professional was used, known as

unobserved automated office blood pressure measurement (UAOBPM). In this technique, after duly instructed, the patient measures their own blood pressure in a room set aside for that purpose. In SPRINT, participants followed a protocol where they waited in a quiet room for five minutes, then an automated device measured their BP three times, with one minute intervals, and recorded the readings. UAOBPM improves BP measurement reproducibility, and the white-coat effect may be significantly lowered or even eliminated.^{171,172} In UAOBPM, readings are similar or lower than those obtained via ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBPM).¹⁷³ However, one cannot forget that conventional office BP measurement is the basis for all currently available clinical and epidemiological data.

For obese individuals, optimum cuff size and shape to fit the patient's arm is critical. Proper cuff choice depends on both the circumference and the shape of the arm.¹⁷⁴ Longer and wider cuffs are required for measurements in these patients to avoid overestimating BP. The forearm approach should be considered valid and may be used in clinical settings for BP measurement when severe obesity makes measurement in the upper arm too challenging (arm circumference greater than 50 cm, for which there are no cuffs available). In these situations, the radial pulse should be auscultated, though there are limitations to that practice.^{175,176} Cone-shaped, wide, short arms that do not fit large cuffs represent a particular challenge for BP measurement. The use of validated heart rate monitors should also be considered in these cases.^{177,178}

3.3. Classification

The BP limits considered normal are arbitrary.^{164,179} The values used to classify BP in adults by using casual or office measurements are shown in Chart 3.4. Individuals are considered hypertensives if SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg. When using office measurements, the hypertension diagnosis should always be validated with repeated readings, under ideal conditions, on at least two visits made days or weeks apart; or more assertively by using out-of-office measurements (ABPM or HBPM), except for patients already presenting with EOD or CV disease.³⁷ Patient classification follows the office BP measure and the highest BP level, either systolic or diastolic.

Individuals with SBP ≥ 140 mm Hg and DBP < 90 mm Hg are classified as having isolated systolic HT, while SBP < 140 mm Hg and DBP ≥ 90 mm Hg is characteristic of isolated diastolic HT. Both isolated systolic HT and isolated diastolic HT have higher rates of white-coat HT (WCH).¹⁸⁰

In the previous Brazilian guidelines,¹⁶⁴ what was then called normal BP is now known as optimum BP, while prehypertension is now divided into normal BP and prehypertension. Individuals with SBP from 130 to 139 and DBP from 85 to 89 mm Hg are now considered prehypertensive, since that population has shown a consistently higher risk of CV disease, coronary artery disease, and stroke than populations with BP between 120 and 129 or 80 and 84 mm Hg. They are also at greater risk of having masked hypertension (MH).^{181,182} Consequently, prehypertensive individuals should be monitored closely.

3.4. Out-of-Office Blood Pressure Measurement

Out-of-office BP may be measured using ABPM or HBPM, following its indications and restrictions.¹⁸³⁻¹⁸⁷ Out-of-office BP measurements should be encouraged. The major advantages and disadvantages of out-of-office BP measurement are summarized in Chart 3.5, while its primary indications, as well as specific indications for HBPM, can be found in Chart 3.6.

ABPM and HBPM should not be mistaken for self-measured blood pressure (SMBP), performed by patients themselves using automated devices, which do not follow any pre-established protocol. The measurements are made at random, at the patient's discretion or as requested by the physician.¹⁸⁸

The COVID-19 pandemic has accelerated the development of telemedicine (televist, telecounseling, and telemonitoring), a change we believe to be irreversible. Currently, the Brazilian Unified Health System (SUS) already provides COVID-19 telecounseling, and supplementary health care services have already adopted it as well. Here, SMBP has the possibility of contributing to diagnosis, follow-up and treatment for hypertensive patients. To that end, this guideline recommends the use of high-quality oscillometric devices, ie, preferably brachial cuff-based devices that have been validated. Wrist blood pressure monitors should be discouraged, but where used, give preference to validated devices that include height and motion sensors. A minimum of seven measurements, performed during a 16- to 72-hour period, is recommended. Thus far, recommended normal values are the same as for HBPM, though specific studies and trials are still needed to compare BP values observed using each technique.^{187,189}

The definition of hypertension by BP at the physician's office is shown on Chart 3.7. Compared to office BP readings, HBPM values are usually low, and the diagnostic threshold for BP is $\geq 130/80$ mm Hg (equivalent to office BP $\geq 140/90$ mm Hg).^{180,190-192} HBPM offers more reproducible BP values and is more strongly related to EOD, particularly left ventricular hypertrophy, and to CV morbidity and mortality than office BP.^{188,193} There is also evidence that HBPM may offer a beneficial effect in terms of adherence to medication and BP control,^{194,195} especially when combined with guidance and counseling.¹⁹⁶ Telemonitoring and smartphone applications may offer additional advantages for HBPM,^{197,198} such as BP measurement reminders and a convenient way to store and edit BP data in a digital report.

ABPM is a better predictor of CV risk and EOD than office BP.¹⁹⁹ In addition, 24-hour ambulatory BP means are better correlated with fatal or nonfatal events,^{200,201} such as fatal and nonfatal coronary events and strokes.²⁰²⁻²⁰⁵

3.5. White-Coat Effect (WCE) and Masking Effect (ME)

The difference in BP between measurements taken at the physician's office and out of it is known as WCE or ME, when the values are positive or negative, respectively. Based on HBPM trials, differences equal to or higher than 15 mm Hg for SBP and/or 9 mm Hg for DBP indicate significant WCE, while differences equal to or lower than -1 mm Hg for SBP and/or DBP indicate significant ME.¹⁸⁰ These scenarios do not change the diagnosis; ie, if the individual is normotensive, they remain normotensive, and if hypertensive, they remain hypertensive. However, it may be useful in identifying individuals at risk of

significant BP differences at and out of the physician's office, which may contribute to better therapeutic management.

3.6. White Coat Hypertension (WCH) and Masked Hypertension (MH)

Several different phenotypes are possible for an HT diagnosis. True normotension (TNT) is defined as normal attended and unattended BP measurements, sustained HT (SHT) when both are abnormal, WCH when BP is high at the physician's office but normal outside it, and MH when BP is normal at the office, but high outside it.^{206,207} Estimated prevalence rates in Brazil can be found in Figure 3.1.^{208,209}

Though the prevalence varies between studies, WCH can be found in approximately 15 to 19% of individuals at the office and up to 30 to 40% of individuals with high BP at the office. It is more common among patients with stage 1 hypertension.²¹⁰⁻²¹²

The presence of EOD and the risk of CV events associated with WCH are lower than in SHT.^{205,213,214} However, compared to TNT, WCH is associated with higher adrenergic activity, higher prevalence of metabolic risk factors, more frequent EOD and higher of developing diabetes mellitus, and progressing to SHT and left ventricular hypertrophy.^{215,216} In WCH, out-of-office BP values tend to be higher than in TNT, which might explain the increased long-term risk of CV events.²¹⁷⁻²²¹

Like WCH, the prevalence of MH may vary significantly across populations. However, overall, MH may be found in approximately 7 to 8% of individuals at the physician's office, and may total circa 15% of normotensives.^{222,223} Several factors can elevate out-of-office BP compared to office BP, such as being older, male, smoking, alcohol consumption, physical activity, exercise-induced hypertension, anxiety, stress, obesity, diabetes mellitus, chronic kidney disease, and family history of HT. MH is associated with dyslipidemia, dysglycemia, EOD, prehypertension, and adrenergic activity and increases the risk of progression to diabetes mellitus and SHT.^{183,185,198,207,224-226} Meta-analyses of prospective studies report that the incidence of CV events is approximately twice as high in MH than in TNT, and comparable to that in HT.^{210,227,228}

3.7. Uncontrolled Masked and White Coat Hypertension

WCH and MH were originally defined for people who were not being treated for HT. However, patients on antihypertensive medications may also have divergent BP behaviors in and out of the physician's office. The following terms are used for patients treated with antihypertensives: uncontrolled masked HT, when BP is controlled at the office, but high out of it; uncontrolled white-coat HT, when BP is high at the office, but normal out of it; uncontrolled sustained HT, when BP is high at and out of the office; and controlled HT, when BP is normal at and out of the office.²¹⁸ Figure 3.2 shows the prevalence rates for these four phenotypes in Brazil.^{213,214}

3.8. Diagnosis and Follow-Up Recommendations

HT is a habitually asymptomatic condition. Therefore, it should be assessed during doctor's visits and as part of structured population-based screening programs. In the

latter, over 50% of HT patients did not know they had the disease.^{229,230} BP should be measured at regular intervals, with frequency determined by BP classification (Figure 3.3). Healthy individuals with optimum office BP (< 120/80 mm Hg) or normal BP (120-129/80-84 mm Hg) should have their BP measured at least once a year and during medical appointments. Patients suffering from prehypertension (130-139/85-89 mm Hg) should have their BP measured annually, or preferably more often than that, due to the high rates of progression to HT. In addition, if MH is suspected, ABPM or HBPM should be deployed to investigate the phenotype.

Since BP may be highly variable, a diagnosis of HT should not be based exclusively on BP values at a single visit, unless it is significantly elevated (stage 3 HT) or there is an established diagnosis of EOD or CV disease. For other patients, repeated BP measurements in subsequent visits to the physician's office should be used to verify persistent high BP as well as to stage the disease. The higher the stage, the more frequent the appointments should be and the shorter the interval between them. Therefore, stages 2 and 3 patients may require more frequent visits (days or weeks apart), while stage 1 patients may require visits after a few months, especially when there is no EOD and CV risk is low.

The guideline recommends the use of out-of-office BP measurements (Figure 3.3) as an alternate strategy for repeated office BP measurements to confirm the HT diagnosis, as long as they are logistically and economically feasible.²³¹ This approach may also generate relevant supplementary clinical information, such as detecting WCH and MH^{213,214,232} (Chart 3.6 and Figure 3.3).

The exercise stress test is not recommended for the diagnostic assessment of HT due to several limitations, including lack of standardization in methods and definitions. Currently, there is no consensus about normal BP response to physical exercise.

3.9. Central Aortic Pressure

Several techniques have enabled the measurement of aortic BP (central BP) using algorithms based on brachial BP readings.^{233,159} Several studies show different reductions for

central BP compared to brachial BP for select antihypertensive medications, and though central BP seems to be a better predictor of CV events than brachial BP, the added prognostic value of measuring central BP still requires more evidence.^{160,234}

Spurious HT (isolated systolic HT in young individuals with normal central BP) seems to be the clearest case for use of central BP (when available) in clinical practice, making it the first indication for central BP measurement. It is found in a small fraction of young individuals, especially male athletes, but it remains unclear whether these patients are at lower CV risk than suggested by conventional BP measurements.²³⁵⁻²³⁷

It should be stressed that the prognostic limitations of central BP are not applicable to other parameters associated with said measurements, such as pulse wave velocity (PWV) and augmentation index (AIx), which have well-established prognostic values.²³⁸

3.10. Genetics and Hypertension

Primary hypertension is a multifactorial, but with a strong genetic component. Family and twin studies have shown 30 to 50% heritability levels.^{239,240} Most of the genetic risk is polygenic, ie, it comes from the contribution of hundreds of DNA variants that, taken together and after interacting with the environment, increase the risk of developing a hypertensive phenotype. A recent study of over 1 million patients showed that DNA variations in over 900 genes are associated with BP control, explaining approximately 27% of the heritability of BP control.²⁴⁰ The study paves the way for the use of gene panels to assess HT risk, which might help guide preventive efforts.

In contrast with primary HT, various forms of secondary HT are caused by heritable single-gene mutations (monogenic HT), such as familial hyperaldosteronism, Liddle's syndrome, congenital adrenal hyperplasia, and hereditary pheochromocytoma and paraganglioma (Chart 3.8).^{240,241} These causes should be investigated in patients suspected of secondary HT. Genetic diagnoses need to take into consideration proper treatment as well as allow genetic counseling for families and early screening for asymptomatic family members.

Guidelines

Recommendation	LR	LE
BP should be classified as optimum, normal, prehypertension or stages 1 to 3, depending on BP measurement at the physician's office.	I	C
HT screening programs are recommended. All adults (≥ 18 years old) should have their BP measured at the physician's office, have their values recorded in their files, and be made aware of their BP. ^{160,234}	I	B
Given the simplicity of measuring BP by oscillometry, using an automated brachial oscillometric device may be preferable to auscultation when both techniques are available.	I	C
Annual BP measurement is indicated if the office BP is $< 140/90$ mm Hg.	I	C
It is recommended that BP be measured in both arms, at least on the first visit, since differences in SBP greater than 15 mm Hg across arms might suggest atheromatous disease and is associated with increased CV risk. ¹⁶⁷	I	A
If a difference in BP < 15 mm Hg is found, it is recommended that all subsequent BP readings use the arms with the highest BP value.	I	C
It is recommended that the HT diagnosis be based on repeated office BP measurements, on multiple visits, except for stage 3 HT and especially for high-risk patients. Three BP measurements should be taken at each appointment, at 1 to 2 minute intervals; additional measurements should only be performed if the first two readings differ by > 10 mm Hg. The patient's BP is the mean of the last two BP readings.	I	C
It is recommended that the HT diagnosis be based on out-of-office BP measurements using ABPM and/or HBPM, as long as these measurement techniques are feasible (logistically and economically).	I	C
Out-of-office BP (ie, ABPM or HBPM) is specifically recommended for various clinical indications, such as identifying WCH and MH, quantifying treatment effects and identifying possible causes of side effects (eg, symptomatic hypotension). ^{164,170,180,201,209}	I	A
Pulse pressure, BP variability and central BP may be considered, but are currently little used in routine clinical practice. They may provide useful additional information in certain circumstances and stand as valuable research instruments.	IIb	C
Genetic testing should be considered in specialized centers for patients suspected of rare monogenic causes of secondary HT or for those with pheochromocytoma. ²⁴⁰⁻²⁴²	IIa	B
Routine genetic testing for hypertensive patients is not recommended.	III	C

ABPM: ambulatory blood pressure monitoring; BP: blood pressure; CV: cardiovascular; HBPM: home blood pressure monitoring; MH: masked hypertension; WCH: white coat hypertension.

Key Takeaways

BP should be classified as optimum, normal, prehypertension or stages 1 to 3, depending on office BP.

HT screening programs are recommended. All adults (≥ 18 years old) should have their BP measured at the physician's office, have their values recorded in their files, and be made aware of their BP.

Annual BP measurement is indicated if the office BP is $< 140/90$ mm Hg.

It is recommended that the HT diagnosis be based on repeated office BP measurements, on multiple visits, or on out-of-office BP measured by ABPM and/or HBPM when either or both are feasible.

Out-of-office BP (ie, ABPM or HBPM) is specifically recommended for various clinical indications, such as identifying WCH and MH, quantifying treatment effects and identifying possible causes of side effects (eg, symptomatic anemia hypotension).

Chart 3.1 – Cuff dimensions by limb circumference

Circumference	Cuff denomination	Cuff width	Bladder length
≤ 6 cm	Newborn	3 cm	6 cm
6-15 cm	Toddler	5 cm	15 cm
16-21 cm	Child	8 cm	21 cm
22-26 cm	Small adult	10 cm	24 cm
27-34 cm	Adult	13 cm	30 cm
35-44 cm	Large adult	16 cm	38 cm
45-52 cm	Thigh	20 cm	42 cm

Source: Malachias et al., 2017.¹⁶⁴

Chart 3.2 – Blood pressure measurement at the physician's office

The patient should seat comfortably in a quiet environment for 5 minutes before BP measurement can begin. Explain the procedure to the individual and instruct them not to talk during the measurement. Possible doubts should be clarified before or after the procedure.

Make sure the patient does or has NOT:

- Have a fuller bladder;
- Exercised within the last 60 minutes;
- Had coffee or alcohol or eaten;
- Smoked within the last 30 minutes.

Three BP measurements should be taken, at 1 to 2 minute intervals; additional measurements should only be performed if the first two readings differ by > 10 mm Hg. Record in the patient's chart the mean of the last two BP readings, without rounding it up or down, and the arm used for the measurement.

Additional measurements may have to be performed for patients with unstable BP due to heart arrhythmias. In patients with AF, auscultatory methods are preferable, since most automated devices have not been validated for BP measurement.*

Use properly sized cuffs for arm circumference.

The cuff should be positioned at heart level. The patient should have their palm up and their clothing should not compress their arm. Patients should have back and forearm supported, legs uncrossed, and feet planted on the ground.

Measure BP in both arms during the first visit, preferably both simultaneously, to detect possible differences between arms. The arm with the higher reading provides the reference value.

In investigating orthostatic hypotension, first measure BP (preferably in supine position, after the patient has been supine for 5 minutes; if the individual is unable to remain in supine position, the measurement may alternately be taken with the patient sitting, though that position is not ideal), then take additional BP readings 1 minute and 3 minutes after the person stands up. BP should be measured at rest and standing for all patients in their first visit and also considered in subsequent visits for older adults, diabetes patients and dysautonomic patients, as well as those on any antihypertensive medication.

Record the heart rate. To rule out arrhythmia, use palpation of the pulse.

Inform the patient of the BP reading.

*AF: atrial fibrillation; BP: blood pressure. *Most automated devices register the highest individual systolic blood pressure reading instead of averaging out several cardiac cycles for AF patients, leading BP to be overestimated.*

Chart 3.3 – Steps of blood pressure measurement

Steps

1. Measure arm circumference at the midpoint between the acromion and the olecranon.
2. Choose cuff sized to match the arm.
3. Place cuff snugly 2 to 3 cm from the cubital fossa.
4. Centralize the compressive part of the cuff on the brachial artery.
5. Estimate BP level based on palpation of the radial pulse.*
6. Palpate the brachial artery on the cubital fossa and place the stethoscope's diaphragm without excessive compression;*
7. Inflate cuff rapidly until the estimated SBP level obtained on palpation is exceeded by 20-30 mm Hg;*
8. Proceed to deflate slowly (2 mm Hg per second).*
9. Determine SBP by auscultation of the first sound (Korotkoff phase I), then slightly increase the deflation velocity.*
10. Determine DBP when the sounds disappear (Korotkoff phase V).*
11. Auscultate until 20-30 mm Hg below the last sound to confirm its disappearance, then proceed to rapid and complete deflation.*
12. If heart beats persist until zero, determine DBP on the muffling of sounds (Korotkoff phase IV) and write down the values of SBP/DBP/zero.*

*DBP: diastolic blood pressure; SBP: systolic blood pressure. * Items performed exclusively in the auscultatory technique*

Guidelines

Chart 3.4 – Classification of blood pressure from in-office measurement, ages 18 and up.

Classification*	SBP (mm Hg)		DBP (mm Hg)
Optimum BP	< 120	and	< 80
Normal BP	120-129	and/or	80-84
Prehypertension	130-139	and/or	85-89
Stage 1 HT	140-159	and/or	90-99
Stage 2 HT	160-179	and/or	100-109
Stage 3 HT	≥ 180	and/or	≥ 110

BP: blood pressure; DBP: diastolic blood pressure; HT: hypertension; SBP: systolic blood pressure. * Classification follows office BP and the highest BP level, either systolic or diastolic. ** Isolated systolic HT, characterized by SBP ≥ 140 mm Hg and DBP < 90 mm Hg, is classified as 1, 2 or 3, according to SBP values at the intervals indicated. *** Isolated diastolic HT, characterized by SBP < 140 mm Hg and DBP ≥ 90 mm Hg, is classified as 1, 2 or 3, according to SBP values at the intervals indicated.

Chart 3.5 – Advantages and disadvantages of out-of-office blood pressure measurement

- Greater number of measurements
- Reflects usual activities of patients
- May identify white-coat HT and masked HT
- Greater patient engagement with diagnosis and follow-up

ABPM

- Night readings
- Allows measurement in real-life conditions
- Use in patients with cognitive impairments and in rare cases of obsessive behavior
- Allows short-term assessment of BP variability
- More robust prognostic evidence
- High cost
- Potentially limited availability
- May be uncomfortable

HBPM

- Low cost and widely available
- Measurement at home may be more relaxed than at the physician's office
- Allows assessment of day-to-day BP variability
- Patient engagement in BP measurement
- Higher adherence to treatment
- Only BP at rest
- Potential measurement error
- No night reading

ABPM: ambulatory blood pressure monitoring; BP: blood pressure; HBPM: home blood pressure monitoring; HT: hypertension.

Chart 3.6 – Indications for ABPM or HBPM

ABPM or HBPM

White-coat HT investigation is more frequent, particularly in the following situations:

- Stage 1 HT at the physician's office
- Very high BP at the physician's office in the absence of EOD

Investigating masked HT is more frequent, particularly in the following situations:

- Prehypertension at the physician's office
- Normal BP at the physician's office for patients with EOD or high-risk CV

Confirmation of resistant HT diagnosis

HT control assessment, especially for high CV risk patients

Individuals with exaggerated BP response to physical exercise

Presence of high variability in office BP

Assessment of symptoms of hypotension during treatment

Specific indications for ABPM:

BP assessment during sleep and/or wakefulness dip/dip (eg suspected nocturnal hypertension, obstructive sleep apnea, chronic kidney disease, diabetes, endocrine HT, or autonomic dysfunction)

Investigation of postural and postprandial hypotension in treated and untreated patients

ABPM: ambulatory blood pressure monitoring; BP: blood pressure; DBP: diastolic blood pressure; HBPM: home blood pressure monitoring; HT: hypertension; SBP: systolic blood pressure.

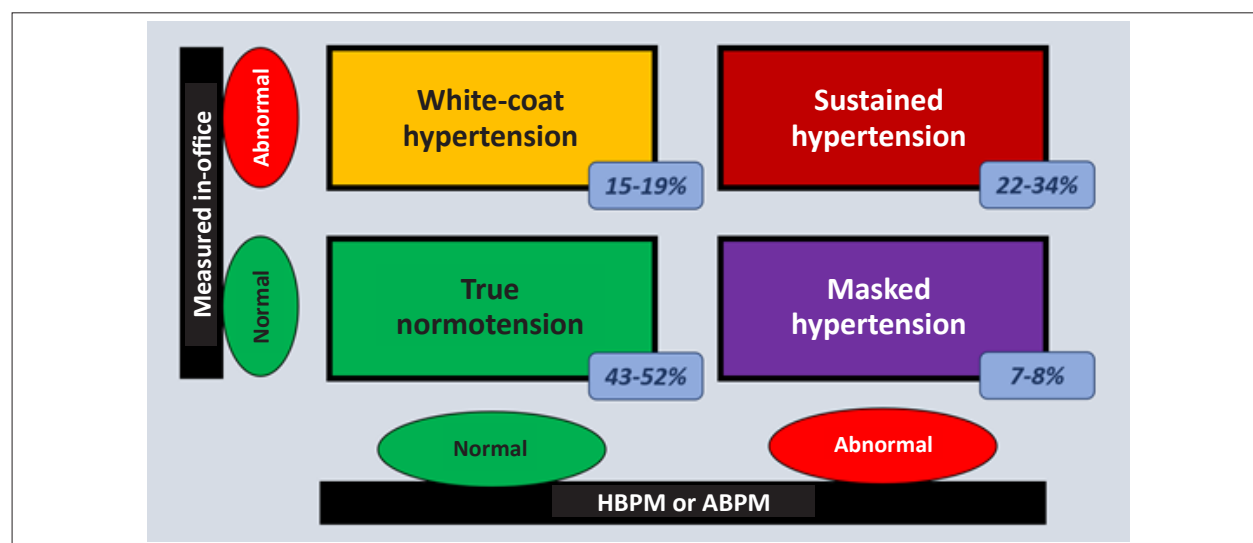
Chart 3.7 – Definition of home blood pressure monitoring according to office blood pressure, ambulatory blood pressure monitoring, and home blood pressure monitoring

Category	SBP (mm Hg)		DBP (mm Hg)
Office BP	≥ 140	and/or	≥ 90
24-hour ABPM	≥ 130	and/or	≥ 80
Daytime	≥ 135	and/or	≥ 85
Sleep	≥ 120	and/or	≥ 70
HBPM	≥ 130	and/or	≥ 80

ABPM: ambulatory blood pressure monitoring; BP: blood pressure; DBP: diastolic blood pressure; HBPM: home blood pressure monitoring; HT: hypertension; SBP: systolic blood pressure.

Chart 3.8 – Causes of monogenic hypertension

Condition	Mode of inheritance	Genes involved
Liddle's Syndrome	Autosomal dominant	SCNN1B and SCNN1G
Congenital adrenal hyperplasia	Autosomal recessive	CYP11B1
	Autosomal recessive	CYP17A1
Apparent mineralocorticoid excess syndrome	Autosomal recessive	HSD11B2
Geller Syndrome	Autosomal dominant	NR3C2
	Autosomal dominant	WNK4
Gordon syndrome (pseudohypoaldosteronism type II)	Autosomal dominant	WNK1
	Autosomal recessive or dominant	KLHL3
	Autosomal dominant	CUL3
Familial hyperaldosteronism type I	Autosomal dominant	CYP11B1
Familial hyperaldosteronism type II	Autosomal dominant	CLCN2
Familial hyperaldosteronism type III	Autosomal dominant	KCNJ5
Familial hyperaldosteronism type IV	Autosomal dominant	CACNA1H

**Figure 3.1 – Possible diagnoses in hypertension (phenotypes).**

ABPM: ambulatory blood pressure monitoring; HBPM: home blood pressure monitoring.

Guidelines

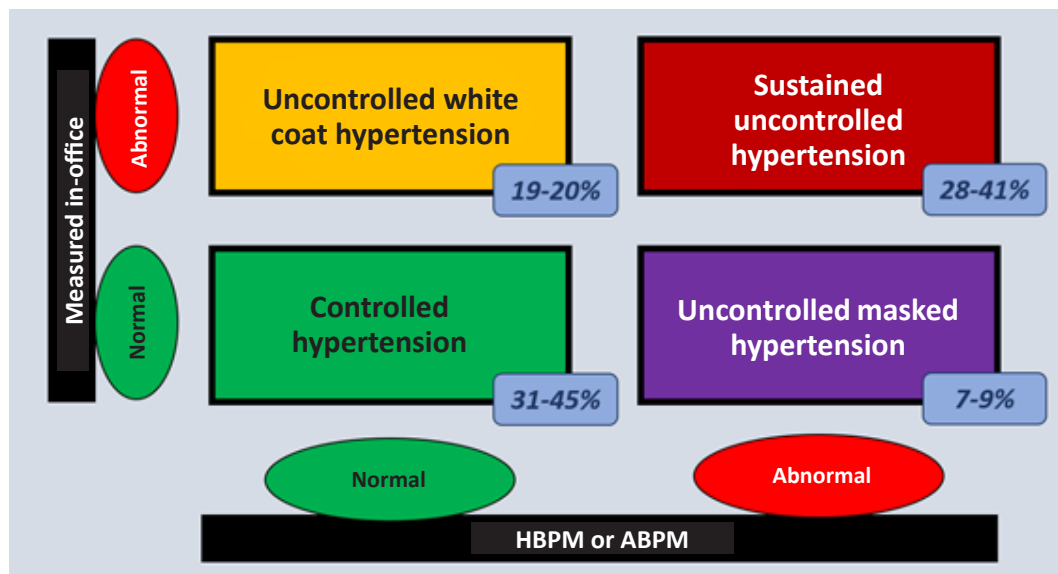


Figure 3.2 – Fenótipos em hipertensos tratados.

MAPA: monitorização ambulatorial da pressão arterial; MRPA: monitorização residencial da pressão arterial.

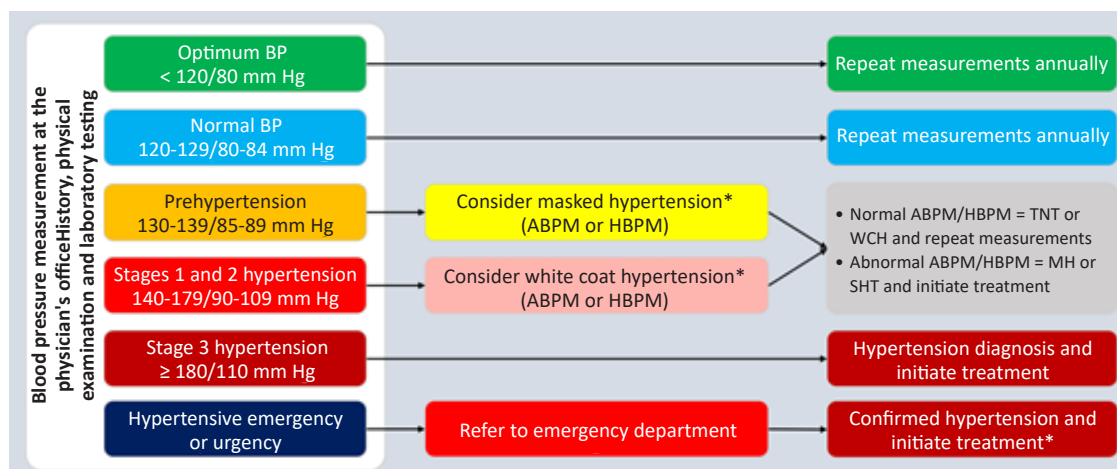


Figure 3.3 – Screening and diagnosis of hypertension.

ABPM: ambulatory blood pressure monitoring; BP: blood pressure; HBPM: home blood pressure monitoring; MH: masked hypertension; SHT: sustained hypertension; TNT: true normotension; WCH: white coat hypertension.

4. Clinical and Complementary Assessment

4.1. Clinical History

The clinical assessment of hypertensive patients should follow the traditional methodology, consisting of taking their hypertensive patient, physical examination, and laboratory tests. Chart 4.1 summarizes the objectives. Following every step of the process will enable physicians to correctly diagnose hypertension (HT) and stratify cardiovascular and renal risks, contributing to a more adequate therapeutic strategy.

4.2. Clinical Assessment

4.2.1. History-Taking

A full patient history should be taken, including mandatory questions about timing of diagnosis and prior antihypertensive treatments (medications and dosage). In addition, symptoms indicating the progress of hypertension, especially the presence of end-organ damage (EOD), should be investigated. It is also important to establish the patient's personal history and to build a timeline to better understand their clinical condition.

Family histories should also be taken to corroborate a diagnosis of primary HT²⁴³ (LR: I; LE: B). During the appointment, the patient should be asked, among others, about the presence of specific cardiovascular disease (CVD) and kidney disease risk factors,²⁴⁴⁻²⁴⁶ comorbidities and biopsychosocial, cultural, and socioeconomic aspects.^{244,245,247} Assessing the use of other nonantihypertensive medications, whether legal or illegal drugs, that might interfere with BP (Chapter 9) is critical, as is investigating the patient's clinical history for signs suggesting secondary causes of HT, as detailed in Chapter 15.

4.3. Physical Examination

A detailed physical examination should be performed, with proper and repeated BP and heart rate (HR) measurements, as described in Chapter 3, as well as the search for signs of EOD and findings that might suggest secondary causes of HT.

Anthropometric data, such as weight, height, as well as body mass index (BMI) calculation,²⁴⁸ and abdominal circumference (AC),²⁴⁸ have normal reference values defined by the *World Obesity Federation* (available online at <https://www.worldobesity.org/>). The assessment should include palpation and auscultation of the heart, carotid arteries, and pulses. Measuring the ankle-brachial index (ABI) is also encouraged, as is fundoscopy.^{249,250} To calculate ABI, divide brachial systolic blood pressure (SBP) by ankle SBP for both the left and the right side. The normal arm/ankle SBP ratio is higher than 0.90. Mild obstruction is characterized by ABI from 0.71 to 0.90; moderate, from 0.41 to 0.70; and severe, from 0.00 to 0.40 (LR: IIa, LE: B). It is an important tool for diagnosing peripheral occlusive atherosclerotic disease and to determine the prognosis for cardiovascular events.²⁵⁰

In some cases, measuring central blood pressure (CBP) in order to detect isolated systolic hypertension in young

individuals (spurious hypertension of youth) may be recommended, since, unlike brachial artery readings, CBP is not high in these situations (LR: IIa, LE: B) (Chapter 3).^{251,252} Chart 4.2 shows a summary of the physical examination.

4.3.1. Basic Laboratory Investigation, Assessment of Subclinical and Clinical End-Organ Damage

The goal of complementary assessment is to detect subclinical or clinical end-organ damage to better stratify cardiovascular (CV) risk. To stratify global CV risk, in addition to classical risk factors (Chart 4.3), other, recently-identified risk factors should also be considered, although not all have been incorporated into clinical scores.^{253,254} Important elements in this investigations include altered glycemia or glycated hemoglobin, abdominal obesity (metabolic syndrome), pulse pressure > 65 mm Hg in older adults, history of pre-eclampsia/eclampsia, and family history of HT (for borderline hypertensive patients).²⁵⁴

Changes in pulse wave velocity (PWV), when available, are indicative of EOD, and may reclassify intermediate CV risk patients as high-risk (LR: IIa, LE: A) (Chapter 2).¹⁵⁶ Basic laboratory assessment (Chart 4.4 and 4.5) should be part of the initial routine for all hypertensive patients.²⁵³ The recommended tests are serum potassium, uric acid, creatinine, glycemia, and lipid profile, as well as urinalysis and an electrocardiogram for possible left ventricular hypertrophy.

To assess renal function, one should obtain the estimated glomerular filtration rate using the *Modification of Diet in Renal Diseases* (MDRD)²⁵⁵ formula or, preferably, the *Chronic Kidney Diseases Epidemiology Collaboration* (CKD-EPI)²⁵⁶ formula, available at <http://mdrd.com/>.

Figure 4.1 shows the estimated glomerular filtration rate (eGFR) accompanied by staging (stages 1 through 5) and prognosis for chronic kidney disease and considering albuminuria levels, according to the *Kidney Diseases Improving Global Outcomes* (KDIGO) guidelines.^{257,258} The colors indicate renal prognosis and management. Green means low risk and good prognosis; yellow, intermediate risk, patient should be monitored; orange, high risk, poor prognosis, mandatory referral to specialist; red, very high risk, poor prognosis, mandatory referral to specialist.

In terms of renal assessment:

It is recommended that the clinical laboratory make the creatinine test results available along with the eGFR results (LR: I, LE: B);

Creatinine clearance results (24 h urine) are not recommended, except for significant changes in muscle mass (amputation), body surface at the extremities and clinical instability (LR: I, LE: B);

It is recommended that the urine protein to albumin ratio be analyzed, in order of importance: urine albumin to creatinine ratio (ACR), urine protein to creatinine ratio (PCR), protein urine test strips with automated or manual reading. It is recommended that clinical laboratories report ACR and PCR for all urine samples and not just their concentrations (LR: I, LE: B).

Guidelines

Key Takeaways

A full medical history and physical examination should always include proper BP measurement, analysis of anthropometric parameters and investigation of signs and symptoms of end-organ impairment and secondary causes of hypertension.

In hypertensive patients, it is important to investigate comorbidities (diabetes mellitus, dyslipidemia, and kidney and thyroid disease, among others) to improve CV risk stratification and treatment.

The routine supplementary tests recommended in this guideline are basic, easily available and easy to interpret, low-cost and mandatory for all patients, at least in their first visit and once a year. Other tests are required for indicated populations.

Investigating end-organ damage, both clinical and subclinical, is essential for fuller therapeutic guidance.

Chart 4.1 – Clinical and laboratory assessment

Perform accurate BP measurements for diagnostic confirmation of HT (Chapter 2)

Ask about family history of HT

Identify associated renal and cardiovascular risk factors

Investigate EOD (subclinical or clinically manifested)

Investigate presence of other diseases

Ask about drugs and medications that may interfere with BP

Apply global CV risk score (Chapter 5)

Screen for signs of secondary HT (Chapter 15)

BP: blood pressure; CV: cardiovascular; EOD: end-organ damage; HT: hypertension.

Chart 4.2 – Physical examination assessment

1. Take repeated, accurate BP measurements in both arms (see Chapter 3)
2. Measure anthropometric parameters: weight, height, HR, AC, and BMI.
3. Look for signs of end-organ damage
4. Investigate signs of endocrine disease, such as Cushing's syndrome and hyper or hypothyroidism
5. Examine cervical region: palpation and auscultation of carotid arteries, check of jugular stasis, and thyroid palpation
6. Cardiovascular system assessment: displaced apex beat and propulsion to palpation; in auscultation, presence of S3 or S4, hyperphonic second heart sound, murmurs, and arrhythmias
7. Assess respiratory system: listen for rales, rhonchi, and wheezing
8. Observe extremities: edemas, upper and lower limb pulses (decreased femoral pulse suggests coarctation of the aorta, aortic disease or aortic arch disease)
9. Abdominal palpation and auscultation: fremitus, bruit, abdominal masses suggestive of polycystic kidney disease and tumors (may suggest secondary causes or EOD)
10. Detect sensory and motor deficits in neurological examination
11. Perform fundoscopy or retinography (when available): identify increased dorsal reflex, arteriolar narrowing, pathological arteriovenous crossings, hemorrhages, exudates, and papilledema (signs of hypertensive retinopathy)

AC: abdominal circumference; BMI: body mass index; BP: blood pressure; HR: heart rate.

Chart 4.3 – Additional cardiovascular risk factors

Age (women > 65 years old and men > 55 years old)
Smoking
Dyslipidemia: fasting triglycerides (TG) > 150 mg/dL; LDL-c > 100 mg/dL; HDL-c < 40 mg/dL
Confirmed diabetes mellitus (DM) (fasting plasma glucose of at least 8 hours $\geq$ 126 mg/dL, random blood glucose $\geq$ 200 mg/dL or HbA1c $\geq$ 6.5%) or pre-diabetes (fasting plasma glucose from 100 to 125 mg/dL or HbA1c from 5.7 to 6.4%)
Family history of premature CVD: in women < 65 and men < 55
Pulse pressure in older adults (PP = SBP – DBP) > 65 mm Hg
Abnormal ABI or PWV
Past pathological history of pre-eclampsia or eclampsia
Central obesity: BMI < 24.9 Kg/m ² (normal); from 25 to 29.9 Kg/m ² (overweight); > 30 Kg/m ² (obesity)
Waist-hip ratio (WHR)
Abdominal circumference = women < 88 cm and men < 102 cm Waist: C = at the midpoint between the last rib and the iliac crest Hip H = at the level of the greater trochanter Calculation (WHR) = women: $WHR \leq 0.85$; men: $WHR \leq 0.95$
Metabolic syndrome profile
<i>ABI: ankle-brachial index; BMI: body mass index; H: hip; PP: pulse pressure; W: waist; WHR: waist-hip ratio.</i>

Chart 4.4 – Routine complementary examinations

Urinalysis (LR: I, LE: C)
Plasma potassium (LR: I, LE: C)
Plasma creatinine (LR: I, LE: B)
Fasting plasma glucose (LR: I, LE: C) and HbA1c (LR: I, LE: C)
Estimated glomerular filtration rate (LR: I, LE: B)
Total cholesterol, HDL-C and serum triglycerides (LR: I, LE: C) *
Plasma uric acid (LR: I, LE: C)
Conventional electrocardiogram (LR: I, LE: B) **

* LDL-C is calculated using the following formula: $LDL-C = \text{total cholesterol} - (\text{HDL-C} + \text{triglycerides}/5)$ (when triglycerides < 400 mg/dL).²⁵⁹ * LDL-C may also be measured in routine laboratory work. ** Sokolow-Lyon criteria for LVH: $SV_1 + RV_{5,6} > 35$ mm – Cornell voltage: $RaVL + SV_3 > 20$ mm (women), > 28 mm (men).^{260, 261}

Guidelines

GFR categories (mL/min/1.73m ²) Description and interval			Persistent albuminuria categories Description and intervals		
			A1 Normal to mildly increased	A2 Moderately increased	A3 Severely increased
			< 30 mg/g < 3 mg/mmol	30-300 mg/g 3-30 mg/mmol	> 300 mg/g > 30 mg/mmol
E1	Normal or high	≥ 90			
E2	Mildly decreased	60-89			
E3a	Mildly to moderately decreased	45-59			
E3b	Moderately to severely decreased	30-44			
E4	Severely decreased	15-29			
E5	End-stage renal disease	≤ 15			

Figure 4.1 – Prognosis for chronic kidney disease by glomerular filtration rate and albuminuria.
CKD: Chronic kidney disease, eGFR: estimated glomerular filtration rate; KDIGO: Kidney Diseases Improving Global Outcomes.

Chart 4.5 – Recommended tests for indicated populations.

Chest X-ray: indicated for follow-up of hypertensive patient in case of clinical suspicion of cardiac involvement (LR: IIa, LE: C) and/or pulmonary involvement and to assess hypertensive patients with aortic involvement for whom an echocardiogram is not available.²⁶²

Echocardiogram: more sensitive than an electrocardiogram to diagnose left ventricular hypertrophy (LVH), adds value in the assessment of the geometry of left atrial hypertrophy and size of the left atrium, as well as analysis of systolic and diastolic function. Indicated when there are signs of LVH in the electrocardiogram or for patients with clinical suspicion of heart failure (LR: IIa, LE: B). LVH is diagnosed when the left ventricular mass adjusted for body surface area is equal to or greater than 116 g/m² for men and 96 g/m² for women.²⁶³

Albuminuria or urine protein/creatinine ratio or urine albumin/creatinine ratio: useful test for diabetic hypertensive patients, patients with metabolic syndrome or two or more risk factors, since it is predictive of fatal and nonfatal cardiovascular events (normal values < 30 mg/g of creatinine (LR: I, LE: B)).²⁶⁴

Carotid ultrasound: indicated in the presence of carotid bruit, signs of cerebrovascular disease, or presence of atherosclerotic disease in other areas. Increased carotid intima-media thickness (IMT) and/or the identification of atherosclerosis plaque formation is predictive of stroke and myocardial infarction, regardless of other CV risk factors. IMT values > 0.9 mm are considered abnormal, as is the finding atherosclerotic plaques (LR: I, LE: A).^{265,266}

Doppler or non-Doppler renal ultrasound: necessary for patients with abdominal masses or abdominal murmur (LR: IIa, LE: B).²⁶⁷

Glycated hemoglobin (HbA1c): indicated when fasting plasma glucose is higher than 99 mg/dL, family history or previous diagnosis of type 2 DM and obesity (LR: IIa, LE: B).²⁶⁸

Exercise stress test: indicated in suspected stable coronary disease, diabetes mellitus or family history of coronary disease in patients with controlled blood pressure (LR: IIa, LE: C).²⁶⁹

ABPM/ HBPM: see indications for methods in Chapter 3 (LR: I, LE: A).¹⁸⁶

Pulse wave velocity (PWV) measurement, when available: indicated for low- to moderate-risk hypertensives, considered a useful method to assess arterial stiffness, ie, vascular damage. PWV values higher than 10m/s are considered abnormal for the general population, but there are adjusted reference values for age and sex deciles available (LR: IIa, LE: A).^{139,270,271}

Brain magnetic nuclear resonance (MNR): indicated in patients with cognitive disorders and dementia to detect silent cerebral infarcts and microbleeds (LR: IIa, LE: C).²⁷²

5. Cardiovascular Risk Stratification

5.1. Introduction

There is a widely established causal, linear, and continuous relation between increased blood pressure (BP) and risk of cardiovascular disease (CVD) for both sexes, all ages, and all ethnic groups.⁸⁵ BP interacts synergically with other CVD risk factors (RFs), and its pro-atherogenic effect is proportional to the number and intensity of these additional factors.^{78,273} CVD is a multifactorial condition, dependent on synergic interactions in the whole causal system responsible for its development. In addition, modest increases in several RFs may trigger greater increases in cardiovascular (CV) risk than sharp increases in a single RF.^{273,274} Therefore, quantifying risk for hypertensive patients, ie, the probability of a given individual developing CVD during a given period, is an essential part of the process and can help guide preventive and treatment strategies.^{37,164,275}

It should be stressed that the impact of hypertension (HT) control is proportional to the absolute individual risk and to the global estimated risk.²⁷⁶⁻²⁷⁸ It is noteworthy that the concept of residual risk represents the magnitude of the risk remaining after traditional risk factors are under control.²⁷⁹ Partial RF control and/or late onset of effective therapeutic measures may be key elements for residual CV risk in hypertensive patients. Despite the lack of tools for the identification of residual risk, it is clear that early and accurate RF control is essential.²⁷⁹ Thus, a comprehensive approach to all RFs is fully justified. To that end, when identified, hypertensive patients should be told about risk factors potentially subject to change in order to improve the efficacy of both pharmacological and nonpharmacological measures.^{37,164,275}

CV risk should not be estimated intuitively or by simply adding up the RFs observed, but rather through the application of methods that take into consideration its complex and multifactorial nature.⁴ The process should be based on equations or algorithms,^{4,280,281} instruments that estimate risk based on multivariate regression models based on population-level studies and are recommended by multiple guidelines worldwide.^{4,280,281} Even experienced physicians make mistakes in over 50% of cases when estimating risk without the aid of equations or algorithms.²⁸²

However, one cannot forget the lack of Brazilian population data for these risk estimate models, making them less accurate for assessing CV in Brazil. In other words, international scores may underestimate risk by failing to consider the most prevalent or relevant RFs in Brazil. To mitigate that limitation and prevent the underdiagnosis of high-risk patients, this guideline recommends the identification of other markers, known as risk-modifying factors, to reassess risk in individuals classified as being at moderate risk (see details below).

CV risk classification depends on BP levels, associated CVRFs, presence of end-organ damage (EOD), structural and/or functional damage from HT to vessels, heart, brain, kidneys, and retina, and/or presence of established CVD or kidney disease.^{37,164,275} Different scoring systems have been developed and applied to classify hypertensives as low, moderate and high CV risk patients.^{37,164,275} However, new biomarkers, precursors,

and predictors still seem necessary to improve risk prediction and lower the difference between calculated risk and event rates, especially in individuals classified as being at moderate risk.²⁸³⁻²⁸⁵ Adding relative versus lifetime risk assessment tools risk advancement periods throughout the life cycle, especially for assessing young individuals at low absolute risk but high relative risk of CVD, as well as in older adults, for whom risk estimates are still challenging due to rapid changes in life expectancy and function in latter years.²⁸⁵

5.2. Additional Risk Stratification (Associated Conditions)

Several factors known to, by themselves, determine or accelerate the onset of CVD, regardless of BP values, can coexist or add to each other in most hypertensive patients.^{37,275,286-288} Associated conditions, whether from their prevalence in the general population or the strength of their association with CV events, should be identified in hypertensive patients by their clinical history, physical examination, and complementary testing.^{37,164,275} Therefore, the examination should look for: a) coexisting RFs in HT (Chart 5.1); b) EOD (Chart 5.2); c) presence of established kidney disease and CVD.

Identifying these conditions is important both to develop an estimate of the risk to which the hypertensive patient is exposed in their current stage and to make sure that controllable RFs will be targeted by adequate therapeutic interventions, as intensive as their degree of risk requires.^{37,164,275} The most prevalent and most easily identifiable RFs should be prioritized, as well as those for which there is solid evidence of association with CV risk (Chart 5.1).

The factors listed in Chart 5.1 need to be taken into accounting when estimating CV risk, in accordance with current diagnostic criteria. Age is linearly correlated with HT and risk of CV complications, such as myocardial infarction (AMI) and stroke, and that linearity is more evident for strokes. For AMI, the level of association rises sharply with sex, beginning at age 55 for men and 65 for women.²⁸⁷ Smoking, quantified by pack-year load, secondhand smoking and other forms of tobacco use, such as cigars, pipes, and vapes, are considered central elements for CV risk. Dyslipidemia is characterized by increased low-density lipoprotein (LDL) or the atherogenic lipoprotein profile obtained by subtracting high-density lipoprotein (HDL) from total cholesterol, ie, non-HDL cholesterol. HDL cholesterol levels are still indicated for risk estimates and has separate thresholds for men and women. High triglycerides (TG) are also characteristic of dyslipidemia, particularly when associated with decreased HDL cholesterol or at levels above 500 mg/dL; in this case, there is indication for specific treatment and pancreatitis should be considered. The criteria for diagnosing diabetes mellitus are fasting plasma glucose ≥ 126 mg/dL; glycated hemoglobin $> 6.5\%$, measured by high-performance liquid chromatography (HPLC); or glucose > 200 mg/dL 2 h after oral glucose overload in oral glucose tolerance test or random blood glucose. Obesity should be considered when body mass index (BMI) is > 30 kg/m² or when abdominal circumference (AC) is > 80 cm in women or > 94 cm in men of European or African descent or > 90 cm in men of Asian descent.²⁸⁹

5.2.1. End-Organ Damage

Risk estimates for hypertensive patients should be supplemented with the investigation of EOD, which is frequent, often underdiagnosed, and usually not included in risk stratification scores. They cause additional increases in CV risk, especially when coexisting in a single individual^{5,6,7} (Chart 5.2).

5.2.2. Presence of Cardiovascular and Renal Disease

The presence of documented cerebrovascular and renal disease determines the increased risk of CV events in hypertensive patients.^{37,164,275,290-292} Cerebrovascular disease should be considered in case of ischemic stroke, brain hemorrhage, or transient ischemic attack. Coronary artery disease includes angina, AMI, silent myocardial ischemia, myocardial revascularization surgery, or prior coronary interventions. Heart failure (HF) with preserved ejection fraction (pEF) or reduced ejection fraction (rEF) should also be considered in manifested cardiovascular disease,^{86,275} as well as atrial fibrillation (AF).²⁹³ Likewise, symptomatic peripheral occlusive atherosclerotic disease (POAD)²⁹⁴ and aortic disease related with aneurysms, hematomas, or ulcerations represent cardiovascular manifestations with major impact on global CV risk. Because of its close association with CV risk, stage 4 or higher chronic kidney disease should be considered an indicator of high risk, identified by estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73m², urine albumin/creatinine ratio in an isolated sample (> 300 mg/g creatinine); and urine protein/creatinine in an isolated sample (> 300 mg/g creatinine). Finally, retinopathy attributable to the hypertensive process, such as hemorrhages, exudates, and papilledema, also indicates high risk.^{37,275}

Chart 5.3 shows the main reasons for performing risk estimates, taking into consideration, in addition to blood pressure levels, the presence of coexisting cardiovascular risk factors, EOD, and kidney and/or cardiovascular disease. These include establishing a reasonably accurate prognostic estimate and distinguishing cases requiring more intensive therapeutic regimens.^{37,275}

Chart 5.4 is especially important for risk stratification for hypertensive patients. It is worth considering that the RFs mentioned above are only those with established epidemiological value, easily obtainable in most clinical settings, and with proven prognostic value. It helps us understand how the progression of risks associated with the presence of different BP levels and presence of RFs, EOD, or cardiovascular and/or kidney disease impact middle-aged individuals.

In moderate-risk patients, tests are recommended when feasible and available, but never in an overgeneralized process, to identify subclinical EOD markers in order to make risk estimates more accurate.^{82,295,296} Echocardiograms to assess LVH, which also record ventricular function parameters, and left ventricular mass index (LVMI) are important (LR: IIa, LE: B), as is albuminuria, preferably in the urine albumin/creatinine ratio, and ABI calculation (LR: IIa, LE: B). Vascular biomarkers added more recently to clinical practice, such as carotid-femoral pulse wave velocity (cfPWV), may also contribute

for the reclassification of CV risk for these individuals (LR: IIa, LE: A),^{296,297} as well as establish a worse prognosis for patients with established CV disease.^{139,298} This aspect is particularly important for young individuals, who have lower relative risk and for whom there is the opportunity to prevent irreversible structural and functional damage to the arterial walls.

Other conditions are also known to influence or change CV risk for hypertensive patients classified as at moderate risk, but have lower discriminative power.^{37,275} Its identification is not recommended for the identification of high-risk patients or for those without any of the coexisting risk factors discussed above (Chart 5.5).

5.3. Assessment of Global Cardiovascular Risk

Global CV risk stratification is not specific for hypertensive patients, and its objective is to determine the risk of a given individual ages 30 to 74 to develop CVD in general over the next 10 years.^{3,4,280,281,299} It should be stressed that the relative impact of HT is one of the highest for any CVRFs, and therefore used in all global risk estimate equations. In addition, CV risk cannot be effectively mitigated without taking into consideration all the elements that determine the clinical course of hypertensive patients. A quick and practical way of calculating global CV risk is to use the Cardiovascular Risk Stratification Calculator recommended and provided by the SBC Atherosclerosis Department on its website, available for Android and iOS devices.³

5.4. Challenges of Cardiovascular Risk Assessment in Hypertension

Several clinical conditions can impact CV risk stratification for hypertensive patients, and age is one of the most important. In the short run, while older patients have higher absolute risk, the young have lower absolute risk even when they have an unfavorable risk profile.³⁷ In the long run or for their lifetime risk, the influence of age on CV risk flips, and longevity loss becomes highest for those who had RFs when young.

Another limitation is the duration of exposure to the disease or RF. Scoring instruments that use binary (yes or no) choices for clinical conditions such as DM and smoking to assess cardiovascular risk do not take into consideration the duration of these conditions. Therefore, patients with longer exposure times have higher CV risk compared to individuals exposed to the same factors for shorter periods.³⁷ This means that incorporating new instruments to assess relative versus lifetime risk and periods of risk increase seem to be necessary, especially for young adults with low absolute risk but high relative risk for CVD.^{280,299} The concepts of “vascular age” and “cardiometabolic age” can be helpful in that strategy.^{300,301}

The influence of the duration of antihypertensive treatment can also impact the risk estimate. In hypertensive patient who have recently started treatment, blood pressure before onset of treatment should be considered, while in patients who have been in treatment for longer periods, current blood pressure readings should be used.³⁷

The timing and value of BP readings to be considered in CV risk stratification and different HT phenotypes should also be taken into account. Therefore, out-of-office BP measurements

are increasingly encouraged. Home measurements, ambulatory blood pressure monitoring (ABPM), and home blood pressure monitoring (HBPM) have led to important complementary information, though office BP readings are still the reference for diagnosis and to assess treatment efficacy.^{37,164,302} To that end, the recommendation for ABPM has been widened to include confirming the diagnosis of HT, considering the higher correlation of ABPM readings with

EOD and cardiovascular morbidity and mortality compared to casual BP measurements.³⁰³ Likewise, different HT patterns, such as masked hypertension, isolated systolic hypertension, and absence of nighttime dipping, or even increased BP during sleep, also seem to lead to different degrees of cardiovascular risk.^{304,305} Thus, these limitations should be taken into consideration when customizing CV risk estimates for hypertensive patients in clinical practice.

Key Takeaways

Over 50% of hypertensive patients have additional CVRFs.

The presence of one or more additional CVRFs increases the risk of coronary, cerebrovascular, renal, and peripheral artery disease in hypertensive patients.

Identifying additional RFs should be part of diagnostic assessments of hypertensive patients, especially when there is family history of CVD.

CV risk should be estimated for all hypertensive patients using a simple scoring system, based on BP levels and the presence of additional RFs and comorbidities (Chart 5.1).

CV risk can be estimated practically and reliably by identifying RFs, such as age > 65, sex (men > women), heart rate (> 80 bpm), increased body weight, diabetes mellitus, high LDL-c, family history of CVD, family history of SHT, smoking, and psychosocial and/or socioeconomic factors; for EOD: presence of LVH, moderate to severe CKD (eGFR < 60 mL/min/1.73m²) or other assessment confirming presence of EOD and prior diseases: CAD, HF, stroke, POAD, AF, and stage 3 or higher CKD.

AF: atrial fibrillation; CKD: chronic kidney disease; CV: cardiovascular; CVD: cardiovascular disease; EOD: end-organ damage; eGFR: estimated glomerular filtration rate; GRS: global risk score; HF: heart failure; LVH: left ventricular hypertrophy; POAD: peripheral occlusive atherosclerotic disease; RF: risk factor.

Chart 5.1 – Coexisting risk factors for hypertension

Male

Age: > 55 years for men and > 65 years for women

Premature CVD in 1st degree relatives (men < 55 years old and women < 65 years old)

Smoking

Dyslipidemia: LDL cholesterol ≥ 100 mg/dL and/or non-HDL cholesterol ≥ 130 mg/dL and/or HDL cholesterol ≤ 40 mg/dL for men and ≤ 46 mg/dL for women and/or TG > 150 mg/dL

Diabetes mellitus

Obesity (BMI ≥ 30 kg/m²)

Chart 5.2 – End-organ damage

Left ventricular hypertrophy

ECG (Sokolow-Lyon index (SV1 + RV5 or RV6) ≥ 35 mm; RaVL ≥ 11 mm; Cornell voltage > 2440 mm.ms or Cornell index > 28 mm in men and > 20 mm in women (LR: I, LE: B)

ECHO: LVMI ≥ 116 g/m² in men or ≥ 96 g/m² in women (LR: IIa, LE: B)

ABI < 0.9 GR (LR: IIa, LE: B)

Stage 3 chronic kidney disease (eGFR between 30 and 60 mL/min/1.73m²)

Albuminuria from 30 to 300 mg/24 h or urinary albumin to creatinine ratio of 30 to 300 mg/g (LR: I, LE: B)

Carotid-femoral PWV > 10 m/s (LR: IIa, LE: A)

ABI: ankle-brachial index; ECG: electrocardiogram; ECHO: echocardiogram; eGFR: estimated glomerular filtration rate; LVMI: left ventricular mass index; PWV: pulse wave velocity.

Guidelines

Chart 5.3 – Reasons to perform risk assessments (LR: I LE: C)

Estimating medium- and long-term risk of cardiovascular events
Determining health care level, such as frequency of service
Determining early timing of pharmacological treatment onset
Determining intensity of control of modifiable risk factors

Chart 5.4 – Hypertension staging by BP level, presence of CVRFs, EOD, or comorbidities

RR, presence of EOD or disease	BP (mm Hg)			
	Prehypertension SBP 130-139 DBP 85-89	Stage 1 SBP 140-159 DBP 90-99	Stage 2 SBP 160-179 DBP 100-109	Stage 3 SBP ≥ 180 DBP > 110
No RF	No additional risk	Low risk	Moderate risk	High Risk
1 or 2 RFs	Low risk	Moderate risk	High Risk	High Risk
≥ 3 RFs	Moderate risk	High Risk	High Risk	High Risk
EOD, stage 3 CVD, DM, CVD	High Risk	High Risk	High Risk	High Risk

BP: blood pressure; CKD: chronic kidney disease; CVD: cardiovascular disease; DBP: diastolic blood pressure; DM: diabetes mellitus; EOD: end-organ damage; RF: risk factor; SBP: systolic blood pressure.

Chart 5.5 – Factors modifying risks for hypertensive patients

Family history or parental history of early-onset hypertension

Very high individual RF, including stage 3 HT
Prior eclampsia/pre-eclampsia
Sleep apnea
Pulse pressure ≥ 60 (in older patients)
Uric acid > 7 mg/dL (men) and > 5.7 mg/dL (women) (LR: I, LE: C)
High-sensitivity C-reactive protein > 2mg/L (LR: I, LE: B)
HR > 80 bpm
Metabolic syndrome*
Sedentary lifestyle
Psychosocial and economic factors
Chronic inflammatory disease

HR: heart rate; HT: hypertension; RF: risk factor. * According to the criteria established by the International Diabetes Federation (IDF), metabolic syndrome requires central obesity, defined as abdominal circumference > 80 cm in women or > 94 cm in men of European or African descent or > 90 cm in men of Asian descent, as well as any two of the following four factors: triglycerides > 150 mg/dL, low HDL-C (< 40 mg/dL in men and < 50 mg/dL in women), hypertension; fasting plasma glucose ≥ 100 mg/dL or previously diagnosed type 2 diabetes mellitus.²⁸⁹

6. Therapeutic Decision and Targets

6.1. Introduction

One of the specific goals of treatment for hypertensive patients is to achieve blood pressure control by hitting a previously established blood-pressure (BP) target. That target should be defined on an individual basis, and always take into account age and presence of cardiovascular disease (CVD) or risk factors (RFs). In general, BP decreases should target BP levels below 140/90 mm Hg, but not lower than 120/70 mm Hg (LR: I, LE: A). In younger individuals without RFs, lower targets, with values below 130/80 mm Hg, are achievable.

6.2. Low- or Moderate-Risk Hypertensive Patients

Cardiovascular (CV) risk estimates are extremely important in hypertensive patients, as they determine possible differences in BP targets. Hypertensive patients with few additional FR should be assessed from two perspectives: hypertensives with significantly high blood pressure levels without other RFs (stage 2 hypertension: moderate risk) and those with smaller BP increases (stage 1 hypertension: low risk).

The benefits of treating hypertensive patients without other associated CV risk factors with significantly high BP readings (> 160 mm Hg) are well established and have long been systematically recommended by Brazilian and international guidelines.^{5,37,164} On the other hand, there is too little scientific evidence from randomized trials justifying treatment for stage 1 hypertensive patients with low CV risk. The reason is that the large number of participants and long follow-up period required mean that a controlled randomized trial with participants with those characteristics would be infeasible. Therefore, meta-analyses of individual data from participants in randomized trials with stage 1 hypertensive patients with no prior CVD can help us determine the best course of action.³⁰⁶⁻³⁰⁸ One such study found that treating low-risk hypertensive patients did not lead to a decrease in coronary artery disease (CAD) outcomes, CV events, or CV mortality in a four- to five-year follow-up period.³⁰⁶ There was, however, a trend of low stroke and total mortality rates, with both decreases clearly achieved as follow-up times grew longer or as more patients were added to the studies. A second meta-analyses, including approximately 9 000 participants from five randomized trials, found that lowering systolic blood pressure (SBP) by 7 mm Hg with pharmacological treatment led to a 34% decrease in composite outcomes (CAD and stroke) and a 19% decrease in all-cause mortality.³⁰⁷ A third study found lower CV disease and mortality when the initial BP was equal to or higher than 140/90 mm Hg, and the same result was not found for lower initial values.³⁰⁸ All these outcomes are supported by a subgroup analysis from the Heart Outcomes Prevention Evaluation (HOPE)-3 trial. In that study, even if stage 1 hypertensive patients were classified as having intermediate CV risk, antihypertensive treatment with a 6 mm Hg mean decrease in SBP led to a 27% decrease in major CV events.³⁰⁹ Based on this date, pharmacological treatment can be initiated for stage 1 hypertensive patient with low cardiovascular risk, combined with nonpharmacological treatment (LR: I, LE: A).

In terms of blood-pressure targets for low CV risk hypertensive patients, there is also too little specific data

from randomized trials. A recent meta-analysis and data from a large observational study suggest that blood-pressure targets below 140/90 mm Hg should be set and achieved for these patients, with larger decreases in CV outcomes attained from SBP readings between 120 and 130 mm Hg.^{85,310} Therefore, for these patients, targets below 140/90 mm Hg are recommended, and closer to 120/80 mm Hg, if tolerated (Chart 6.1) (LR: I, LE: B).

6.3. High-Risk Hypertensive Patients

In general, hypertensive patients with three or more RFs, diabetic patients, those with end-organ damage (EOD), CV disease, or kidney disease are considered to be at high risk. In clinical practice, the most frequent examples of individuals with high CV risk are hypertensive patients with CAD, prior history of stroke, heart failure and chronic renal failure (CRF), and HT associated with diabetes mellitus (DM). These comorbidities are discussed in Chapter 10 (*Associated Clinical Conditions*), but the targets for each of these clinical situations are discussed below. Keep in mind that high risk depends not only on RFs and EOD, but also on HT staging, as shown in Chart 5.4, and a patient may have RF or EOD but also have stage 3 HT (Chart 6.1).

6.4. Hypertensive Patients with Coronary Disease

HT is an important independent RF for the onset of myocardial ischemia. Before age 50, diastolic BP (DBP) is the main predictor for CAD risk, while SBP is more important after age 60.³¹¹ In older populations, DBP is inversely related with CAD risk, and pulse pressure becomes a stronger predictor of CAD.³¹¹ In a meta-analysis including nearly 1 million adults, fatal CAD was correlated with BP levels equal to and higher than 115/75 mm Hg for all ages.⁷⁸ In that case, antihypertensive treatment for CAD patients should result in BP $< 130/80$ mm Hg, but no lower than 120/70 mm Hg. In patients with evidence of myocardial ischemia, DBP should be cautiously lowered to 70 mm Hg, especially in diabetic patients and in the very old.³¹² Lowering SBP in older patients with CAD and high pulse pressure requires great care, since they may lead to very low DBP values and trigger myocardial ischemia.³¹³

6.5. Hypertensive Patients with History of Stroke

HT is the most important RF for ischemic and hemorrhagic stroke and is directly related to blood pressure levels. In younger individuals with no history of established CV or renal disease, keeping BP within the normal or optimum range, targeting a BP level of 120/80 mm Hg, may be the most effective for of primary prevention for cerebrovascular disease. For those with one or more prior strokes, the most adequate target for secondary prevention should be assessed according to type of stroke and post-event time (Table 10.2). In chronic cases of secondary prevention, keeping SBP from 120 to 130 mm Hg is recommended (LR: I, LE: A).³¹⁴ For older adults or those with associated coronary disease, a relatively common scenario, the J-curve phenomenon should be taken into consideration when BP falls below 120/70 mm Hg, with higher risk of CV events and mortality.³¹⁵

6.6. Hypertensive Heart Failure Patients

Hypertension is considered a risk factor for both forms of heart failure, ie, with reduced ejection fraction and with preserved ejection fraction. Adequate treatment for HT lowers the incidence of HF. No clinical trials specifically for the HF population have compared different treatment goals. Therefore, recommendations are extrapolated from the evidence from other high-risk populations, for which lowering BP has been shown to be most protective against CV events, though with potentially increased side effects. In patients already suffering from HF with reduced ejection fraction, blood pressure control decreases mortality and readmission rates for cardiac decompensation. The proper target for this population is $< 130/80$ mm Hg, but taking care to keep it above $120/70$ mm Hg.³¹⁶ In patients with preserved ejection fraction, the best form of treatment remains uncertain, so the recommended treatment strategy is similar to that for patients with reduced ejection fraction.^{317,318}

6.7. Hypertensive Patients with Chronic Kidney Disease (CKD)

Most CKD patients have high BP, which increases the risk of CV diseases, CKD, and death. The Systolic Blood Pressure Intervention Trial (SPRINT) study concluded that systolic BP < 120 mm Hg lowered the risk of CV disease and mortality for nondiabetic adults with high CV risk, many of whom have CKD. However, it could not halt the progression of CKD.³¹⁹ Notoriously, in that study, BP was measured using automated devices, frequently unattended, which usually results in lower readings than office BP measurements.^{320,321} The absolute decrease in risk may be greater for patients with albuminuria due to the strong association between albuminuria and kidney and CV disease, but the effects of intensive decreases in BP on the risk of CVD seem to be similar by albuminuria level.^{322,323} Current evidence indicates a BP target of $< 130/80$ mm Hg for CKD patients, regardless of DM.^{275,324,325} In patients with end-stage CKD, the benefits of intensive BP control are uncertain due to their short duration and to hemodynamic effects possibly leading to greater decreases in glomerular filtration rate (GFR). Regardless of targets, BP decreases in CKD patients always requires attention to proper BP measurements and monitoring adverse events, especially electrolyte abnormalities and decreases in GFR.³²⁵

6.8. Diabetic Hypertensive Patients

In hypertensive DM patients, morbidity and mortality prevention comes from glycemic control, BP normalization, and lowering other CV risk factors.³²⁶ Keeping BP under control is keep for renal protection in diabetic individuals, as it lowers albuminuria, in addition to its importance in lowering the risk of stroke and left ventricular hypertrophy (LVH).^{327,328} Evidence from randomized controlled trials, meta-analyses and observational studies with hypertensive diabetes patients shows that lowering SBP to 130 - 139 mm Hg, with values closer to the lower bound of 130 mm Hg, effectively protects against CV and renal complications.^{307,329} DBP may be lowered to 70 - 79 mm Hg without compromising individual protection and safety. On the other hand, there is no conclusive data indicating that lowering SBP to < 130 mm Hg leads to higher CV and renal protection. SBP values < 120 mm Hg should be avoided. Therefore, for diabetic patients, the recommended target is $< 130/80$ mm Hg (LR: IIa, LE: B).

Achieving a lower SBP target implies the need for a larger number of antihypertensive medications, increasing the risk of severe adverse effects.³³⁰ In practice, ideal BP targets can vary across diabetic hypertensive patients by age and presence of EOD. For instance, there is no data available for recent-onset diabetes patients with no complications and, therefore, relatively low CV and renal risks. In these cases, very low blood pressure levels may be more easily tolerated and result in greater medium- and long-term benefits. Overall, BP control is harder for patients with diabetes than for patients without diabetes. In addition, diabetic hypertensive patients often have satisfactory office BP levels, but high ABPM or HBPM readings, characterizing masked hypertension. This reinforces the need for out-of-office BP measurement in order to better assess BP control in diabetic hypertensive patients.³³¹

6.9. Older Hypertensive Patients

The complexities of older hypertensive patients are discussed in Chapter 14. BP targets for older populations should consider functional status, frailty and comorbidities in addition to chronological age (≥ 60 in low-income countries and ≥ 65 in all others, according to most international associations).^{37,275} Therefore, the therapeutic goal should balance the potential benefits and harm from BP targets.

In most clinical trials that show the benefit of treating BP in older patients, the SBP target ranged from 140 to 150 mm Hg, with greater decreases in deaths and CV events.^{37,332} In the HYVET trial, which included active and nonfrail patients over 80 years old, in addition to lowering SBP < 150 mm Hg (mean: 144 mm Hg), there were significant decreases in mortality, fatal strokes, and HF.³³³ In a meta-analysis and systematic review of nine studies, the authors found robust evidence that decreases $< 150/90$ mm Hg lower mortality and fewer strokes and cardiac events in older adults.³³⁴ However, recent clinical trials have found evidence for benefits from lower BP targets for older patients.^{87,335} In the SPRINT trial subgroup consisting of individuals over age 75 ,⁸⁷ the intensive treatment group that achieved a mean target BP level of $124/62$ mm Hg had significant decreases in CV events and HF as well as all-cause mortality compared to the group with a less intensive target, for which the average BP level achieved was $135/67$ mm Hg. That study suggests that more intensive treatment may be beneficial even for frailer older adults, but the incidence of falls was higher, as was the incidence of impaired kidney function, in the more intensive blood pressure control group. Another relevant data point from the SPRINT trial is that BP measurements were unsupervised, and these readings tend to be lower than those obtained with conventional methods. Therefore, the target achieved is equivalent to BP values from 130 to 139 mm Hg when compared to readings from previous studies.³²¹ In another meta-analysis, Bavish et al.³³⁵ showed that more aggressive BP control for patients ≥ 65 years old led to greater decreases in CV events, but it has several methodological restrictions and found greater rates of renal failure in the more intensive control group.

Overall, recommended targets for Brazilian patients ≥ 60 years old is to achieve levels matching their global condition (healthy or frail), as shown in both Chart 6.2 and Chapter 14. In older adults, targets should be treated individually, taking into account patients' quality of life, risk of falls, frailty, independence, and presence of comorbidities.

Key Takeaways

In low to moderate CV risk hypertensive patients, the treatment goal is to achieve values below 140/90 mm Hg.

In hypertensives with CAD, the therapeutic target is to have BP < 130/80 mm Hg, but diastolic BP should be kept above 70 mm Hg.

For hypertensive patients with HF or who have had a stroke, antihypertensive treatment should be titrated until achieving the target of BP < 130/80 mm Hg, but the presence of CAD and advanced age, both common in that scenario, limits the ability to lower BP down to 120/70 mm Hg.

In hypertensive patients with CKD, the treatment goal is BP < 130/80 mm Hg, but always monitoring patients for adverse events, especially impaired kidney function and electrolyte abnormalities.

Hypertension treatment in diabetic patients should try to keep BP levels < 130/80 mm Hg, but avoid sharp decreases in BP to levels below 120/70 mm Hg.

Chart 6.1 – General blood-pressure targets for antihypertensive treatment

Target	Cardiovascular risk	
	Low or moderate	High
Systolic blood pressure (mm Hg)	< 140	120-129
Diastolic blood pressure (mm Hg)	< 90	70-79

Chart 6.2 – Treatment goals for older adults considering global condition and office blood pressure measurement.

Global condition ¹	Office SBP		Office DBP	
	Treatment threshold	Blood-pressure target ^{4, 5}	Treatment threshold	Target ⁸
Healthy ²	≥140 (I, A)	130-139 (I, A) ⁶	≥90	70-79
Frail older adults ³	≥160 (I, C)	140-149 (I, C) ⁷	≥90	70-79

1: functional status is more important than chronological age; 2: including light frailty; 3: moderate to severe frailty; 4: including older adults with comorbidities: DM, CAD, CKD, stroke/TIA (not acute stage); 5: actively assess tolerability, including possible atypical symptoms; 6: stricter target (125-135 mm Hg) may be achieved in selected cases, especially for motivated older adults, < 80 years old, with optimum treatment tolerability; 7: higher limits in case of limited survival and absence of symptoms. BP reductions should be gradual; 8: DBP = avoid < 65-70 mm Hg in clinically manifested CAD patients.

7. Multidisciplinary Team

7.1. The Importance of a Multidisciplinary Approach to Hypertension Control

Uncontrolled hypertension (HT) remains a widely prevalent cardiovascular risk factor (CVRF) in Brazil and throughout the world. Various Brazilian and international studies have consistently shown the superiority of blood pressure (BP) control using a multidisciplinary team approach when compared to conventional treatment, including higher quality care, higher adherence and therapeutic success rates, fewer CVRFs, and lower CV morbidity and mortality.³³⁶⁻³⁴¹ Shared patient care and decision-making are associated with lower costs and better results in HT treatment.^{342,343}

Different objectives require different strategies, including patient-centered care, integration between multiple professionals, shared goals and targets, and collaborative decision-making with patient participation.³⁴⁴ A Brazilian retrospective longitudinal study with the goal of evaluating the effect of multidisciplinary care in hypertensive patients age 80 and older ($n = 71$), treated by a specialized service for an average of 15.2 years, found lower BP values, increased BP control rates and treatment optimization.³⁴⁵

A systematic review of 80 U.S. studies from 1980 to 2012 showed the efficacy of team-based care. There was a 12% increase in BP control rates, with median systolic BP (SBP) decrease of -5.4 mm Hg and median diastolic BP (DBP) decrease of -1.8 mm Hg, especially when the team included nurses and pharmacists. These results were found in various multidisciplinary setups and for various American population groups.³⁴⁶

A multidisciplinary team is established through actions that integrate the contributions from all of its members. The spatial element is not the single determinant of this unit; more important is the practice of developing joint actions, where each discipline acts as an independent agent in its own realm, but always acknowledging and collaborating with the actions of other team members.

Multidisciplinary work has been used successfully in primary³⁴⁷, secondary,³³⁶ and tertiary³⁴¹ health care settings. The high complexity of professional activities may drive them away from joint efforts. On the other hand, it is in health promotion and in the level of primary care that we find the greatest potential for integration and where team performance is most effectively embodied. Teamwork has advantages such as encouraging patients to reproduce knowledge and attitudes, favoring research activities in care, and providing opportunities for growth for team members and, consequently, for the institutions themselves.^{337,343, 348-350}

Deploying a multidisciplinary approach requires organizational change at the health care system level, also important in home care settings.³³⁶ A multidisciplinary approach to HT has level of recommendation I and level of evidence A (Chart 7.1).³⁵¹ Therefore, health care becomes a fundamentally collective and complex form of work, requiring interdisciplinarity and multidisciplinary.^{341,347,352} Some duties and responsibilities are shared by all team members, others are specific to each role (LR: I, LE: A).

7.2. Team Composition and Work

7.2.1. Medical Professional: Specific Actions

General practitioners are involved in primary care, while cardiologists, nephrologists, and hypertension specialists are present at the other levels. The activities specific to physicians are as follows:³⁴¹

- Medical visit (detailed in Chapter 4).
- Responsible for diagnosis, risk stratification, and prescription of pharmacological and nonpharmacological therapy.
- Clinical assessment of patients at least twice a year.
- Referral and counter-referral within the health care system.

In addition to physicians, professionals from various health care disciplines (nurses, pharmacists, social workers, nutritionists, physical education professionals, physical therapists, educators, psychologists) have established multidisciplinary teams to provide care for hypertensive patients for several decades in developed countries.^{353,354}

7.2.2. Nursing Professional: Specific Actions

The activities specific to nurses are as follows:

- Performing patient intake, identifying alongside users the various obstacles and barriers in their daily lives, and encouraging the coping process.
- Enabling people to increase their control over factors impacting self-care, improving their health. Advanced communication skills, behavior change techniques, patient education, and counseling skills are key elements to improve and enhance health care systems, necessary to help patients with chronic conditions.³⁵⁵ The Brazilian Ministry of Health stresses that developing actions focused on health promotion and prevention of noncommunicable disease (NCD), especially HT and diabetes mellitus (DM), is an enormous challenge.³⁵⁶
- Encouraging self-care.
- Planning strategies to promote and assess patient adherence to prescribed behaviors using educational, motivational, cognitive and technological approaches.^{344, 357-361}
- Promoting educational health-literacy initiatives for users.^{344, 362}
- Home visits to reinforce medication use and help manage care and/or technologies to promote proper use, such as helping users establish medication intake habits and routines.^{363, 364}

7.2.2.1. Nursing-Specific Actions in Primary Care

Teams working in basic care should try to follow the principle of “person-centered care,” in which individuals are the main agents of personalized care. Professionals should help users develop the knowledge, aptitudes, competences and trust needed to more effectively manage and make informed decisions about their own health. Management plans are designed for people, according to their needs and their possibilities to pursue a full and independent lifestyle. To

that end, the Ministry of Health published Ordinance 2.436, dated September 21, 2017,³⁶⁵ establishing guidelines for the actions and activities of nursing staff, such as:

- Providing health care services to the individuals and families serve by the team and, when indicated or required, at homes and/or other community spaces (schools, associations, etc.) at every step of patients' life cycles.
- Performing nursing visits and procedures, requesting supplementary tests and prescribing medication in accordance with protocol, clinical and therapeutic guidelines and other technical standards, as established by federal, state, municipal or Federal District managers, in accordance with legislation and regulations.
- Performing and/or supervising patient intake with qualified listening and risk classification, following established procedures.
- Performing risk stratification and developing a care plan for individuals with chronic conditions in their territory alongside other team members.
- Performing group activities and referring users to other services, when necessary, following the flow rules established by the local health care network.
- Planning, managing and assessing the actions of nursing technicians and assistants, community health workers (CHW), and endemic disease control agents together with other team members.³⁶⁵
- Supervising the actions of nursing technicians/assistants and CHW.
- Implementing and updating routines, protocols, and flows connected to their area of expertise at their primary health care unit.
- Performing other duties under their purview in accordance with legislation.

7.2.3. Nutrition Professional: Specific Actions

A recent meta-analysis³⁶⁶ showed that nutritional counseling is more effective in lowering BP when provided by a multidisciplinary team including a nutritionist. In primary care, dietetic consultations were found to be the most effective in improving diet quality.³⁶⁷

7.2.3.1. Dietetic Consultation^{367,368}

Visits to nutritionists should include the following items:

- Nutritional history with an assessment of eating routine, number of meals, meal times, types and quantity of food, and frequency of cardioprotective foods.
- Anthropometric assessment: height, weight, and abdominal circumference measurement and body mass index calculation.
- Prescribe and guide diet based on medical diagnosis and laboratory examinations.
- Monitor diet changes and anthropometric evolution.
- Take part in actions involving the population.

7.2.3.2. Collective Actions by Nutritionists

The following actions are recommended:

- Nutritional guidance should center of impactful changes in BP reduction: weight loss,^{369,370} increased intake of fruits and vegetables,³⁷¹⁻³⁷³ and lower sodium intake.^{374, 375}
- Currently, the use of free technological resources in nutrition represent an important large-scale information resource and should be encouraged.^{376, 377}

7.2.4. Physical Education Professional: Specific Actions

Sedentary behavior (time sitting, watching TV or at the cellphone or computer) and physical inactivity (physical activity habits below recommended levels) represent a major public health issue, as they increase treatment costs and lower life expectancy.³⁷⁸⁻³⁸⁰ Physical education professionals have the task of applying the recommendations found in Chapter 8 to minimize these behaviors. To that end, the professional should:

- Recommend less sedentary behavior in adult and adolescent populations.
- Encourage meeting minimum physical activity (PA) recommendations for the whole population through the collective actions detailed below. Practicing these activities contributes to lowering cardiovascular mortality even in case of sedentary behavior.³⁸¹
- Plan, teach and supervise physical exercise (PE) programs, in person or at a distance, individually or in groups, matching local networks and the specific characteristics of each individual. Professionals should make use of technological resources (cellphones, Internet, video games, videos, etc.) to encourage participation, monitor the frequency and intensity of exercises, and teach individuals how to increase their daily regular physical activity levels;
- Perform pre-participation assessments, indicate prior medical evaluation for recommended cases, and perform regular reassessments to verify the effectiveness of physical activity practices and adjust them as they evolve.

7.2.4.1. Collective Actions by Physical Education and Physical Therapy Professionals

- Within multidisciplinary teams, developing community-based PA should be encouraged, through patients and representatives from the community and civil society organizations, given that leisure activities improve quality of life for the community.³⁸²
- As team members, physical education professionals should use positive results to show that treating and preventing HT depends on a combination of decreasing sedentary behavior and increasing physical activity with other factors, such as a healthy diet, weight loss, less stress, decreased salt and alcohol intake, smoking cessation, etc. In addition, adherence to pharmacological treatment and frequent BP readings should be encouraged in order to help control the disease.
- The strategy of establishing Leagues and Associations of people who suffer from HT helps increase patients' adherence to treatment, and these professionals could join the health care teams working alongside these institutions.

Guidelines

- One-off activities, such as Hypertension Prevention Campaigns and Fight Against Hypertension Campaigns, are important and efficient strategies to help patients learn about their health. Physical education and physical therapy professionals have an important role in this setting.

7.3. Multidisciplinary Team Actions

At the primary and secondary care level, in addition to physicians, the multidisciplinary teams can include nurses, nursing technician/assistants, nutritionists, psychologists, social workers, physical education professionals, physical therapists, pharmacists, music therapists, managerial staff, and community health workers, though not all role are required before the team can act.^{383,384}

According to the National Primary Care Policy (Ordinance 2.436, dated September 21, 2017), defines, in Article 2, that “primary care is the set of individual, familial and collective actions that involve the promotion, prevention, protection, diagnosis, treatment, rehabilitation, damage reduction, palliative care, and surveillance, based on practices of comprehensive care and qualified management, performed by a multidisciplinary team and directed toward the population of a given territory over which the teams assume responsibility.”³⁶⁵

Role overlaps can be minimized by establishing clear rules and working on group harmony. Keep in mind that the education

and attitude changes are slow process, and that standardized, clear, objective and balanced communication is critical to achieve one's goals.³⁴³ Team members should work within the boundaries of their specific roles and education, as determined by guidelines and their respective boards. The individual actions of other team members should also be acknowledged.^{347,384}

Multidisciplinary teams have been used to treat hypertensive patients in developed countries for several decades.^{341,348,350,385} Educational and therapeutic actions may involve groups of patients, family members and the community as a whole, and the methods deployed should always take into consideration the specificities of local and regional societies and cultures. Modern approaches may involve social media and distance education techniques.^{338,351,357,362,386,387} Examples of the work of patient-centered multidisciplinary teams, with evidence of better BP control, can be found in Chart 7.1.

In a recent analysis on the future of HT, Dzau & Balatbat³⁸⁸ state that, to this day, care delivery for hypertensive patients is fragmented, service providers are not aligned, and the information is siloed, and that better health care coordination and integration across different care settings and providers is needed. They also claim that, in the future, controlling or preventing HT will depend on the successful convergence of advances in digital, biotechnological, and biomedical sciences, with a special role for multidisciplinary work.³⁸⁸

Key Takeaways

In primary care for hypertensive patients, physicians are responsible for diagnosis, risk stratification, and pharmacological and nonpharmacological therapeutic management, at least twice a year.

At the population level, the most important guidelines are to keep body weight within the reference range, increase intake of fruits and vegetables, and lower sodium intake.

In multidisciplinary teams, physical education professionals should recommend decreased sedentary behavior and encourage individuals to meet minimum physical activity requirements in order to acquire healthy habits and improve quality of life for the community.

Nursing care should be person-centered, making basic information more accessible and understandable and aiding individual and collective self-care decision-making through nursing visits, home visits, and educational group activities.

Strategies for patient-centered multidisciplinary teams, with evidence of better BP control, should be deployed by multidisciplinary teams themselves.

Chart 7.1 – Strategies for patient-centered multidisciplinary teams

Strategies	Description	Examples	Team Member
Patient Education	Educational or interactive approach to inform and educate patients	In-person educational sessions ³⁸⁹ In-person print material ^{389, 390} Mailed print material ³⁹⁰ Audiovisual media and Distance education ³⁹¹	PHY, NUR, PHARM, NUT, PSY, CHW
Social support	Engagement of family members, friends, or other individuals to help patients take medications as prescribed	Support group meetings ^{347, 350} Family education ³⁴⁸	FAM, FR, CT, CHW, SS
Patient literacy and motivation	Motivating patients to take their medication as prescribed and eliminate obstacles that negatively impact that motivation	Motivational interventions ^{386, 389} Implement health literacy initiatives ^{362, 392, 393}	PHY, NUR, NUT, PSY PE, PT, FR, CT, FAM
BP self-monitoring and technology use	Engage patients in monitoring BP and adhering to treatment	Self-measured BP ³⁹¹ Home BP monitoring ^{394, 395} BP telemonitoring ^{343, 390, 396, 397}	PHY, NUR, PAT, FAM, CT, CHW
Communication or interaction with service providers and among team members	Improving communication between patients and multidisciplinary team and other service providers and among team members	Training communication skills between patients and multidisciplinary team and among team members ³⁹⁰ Interactive digital interventions ^{350, 358, 359, 398}	PHY, NUR, NUT, PE, PT, PST, SS, CHW
Facilitating access to health care services	Facilitating scheduling of appointments at times compatible with patient needs	Patients from out of town Older adults depending on accompaniment by third parties ^{345, 399}	CHW, SS

CHW: community health worker; CT: caretaker; FAM: family member; FR: Friend; NUR: nurse; NUT: nutritionist; PE: physical education professional; PHARM: pharmacist; PHY: physician; PSY: psychologist; PT: physical therapist; SS: social worker; PAT: patient. Source: Peacock & Krousel-Wood, 2016.³⁴⁴

8. Nonpharmacological Treatment

8.1. Introduction

High blood pressure (BP), smoking, obesity, unhealthy diets, and insufficient physical activity are established cardiovascular risk factors (CVRFs) and the target of interventions for hypertension (HT) control. In recent years, unconventional therapies have been investigated, involving the adoption of slow breathing, music therapy, and spirituality. In this chapter on nonpharmacological treatment (NPT), we discuss the evidence behind recommendations for smoking, eating habits, sodium, potassium, dairy, chocolate and cocoa products, vitamin D, supplements and substitutes, weight loss, alcohol consumption, physical activity and exercise, slow breathing, stress control, and spirituality and religiosity.

8.2. Smoking

Smoking remains one of the most important CVRFs, and in addition to cigarettes, the use of cigars, cigarillos, pipes, hookahs and vapes remains particularly high in certain countries and is associated with increased CV risk⁴⁰⁰ (LR: I, LE: A). In Brazil, smoking has trended downward in the last 15 years, but the decrease has not been uniformly distributed⁴⁰¹ (LR: IIa, LE: B). Smoking has considerable potential to cause damage, such as accelerating atherothrombotic processes and temporarily increasing BP. On average, tobacco use increases BP by 5 to 10 mm Hg,⁴⁰² but there are no studies showing the beneficial effects of smoking cessation on HT control. Regardless, cessation should be emphasized due to the risk of CV disease and neoplasia.⁴⁰³ Medications for smoking cessation (such as sustained-release bupropion, varenicline,

nicotine gum, drops, nasal spray, and patches) are effective in helping smokers quit⁴⁰⁴ (LR: IIa, LE: B).

8.3. Dietary Patterns

Healthy eating patterns are associated with lower BP. The DASH (Dietary Approaches to Stop Hypertension) diet is capable of lowering BP, with the effect attributed to the increase in fruit, vegetable, low-fat dairy and whole-grain intake, as well moderate consumption of nuts and lower fat, candy, sugary beverages, and red meat. The hypotensive effect is due more to the dietary pattern (Chart 8.1) than to its individual components—high sodium, calcium, magnesium and fiber content, with lower levels of cholesterol and total and saturated fat^{405, 406} (LR: I, LE: A). The association between the DASH diet with sodium restriction⁴⁰⁶ has resulted in a decrease in systolic BP (SBP) of 11.5 mm Hg for hypertensive individuals and 7.1 mm Hg for normotensives compared to a high-sodium diet. Meta-analyses of randomized controlled trials confirm the BP reduction effect^{406, 407} (LR: I, LE: A). Some studies suggest that adherence to the DASH diet is associated with lower risk of stroke^{408, 409} (LR: IIa, LE: B), cardiovascular mortality⁴¹⁰ (LR: I, LE: A) and kidney disease⁴¹¹ (LR: I, LE: A).

Like DASH, the Mediterranean diet is rich in fruits, vegetables, and whole grains and low in red meat. It has a high fat content due to the large amounts of olive oil (source of monounsaturated fatty acids) and includes the consumption of fish and nuts, as well moderate intake of red wine⁴¹² (LR: IIa, LE: B). The diet decreases the risk of cardiovascular issues^{413, 414} (LR: IIa, LE: A), but its effects on blood pressure are modest⁴¹⁴⁻⁴¹⁷ (LR: IIa, LE: B).

8.4. Sodium Intake

Worldwide habitual sodium intake is estimated at 4 g/day⁴¹⁸ (LR: IIa, LE: B), while the recommended intake for hypertensive individuals and for the general population is 2 g/day⁴¹⁹ (LR: I, LE: A). Not to depend on individual adherence to sodium restriction, which decreases in the long run, governments are now working with the food industry to lower sodium content in their products. Epidemiological data show that sodium intake is directly associated with high BP, and randomized controlled trials have shown the hypotensive effect of sodium restriction. The proof of concept is based on the dose-response curve, showing that even a small decrease in sodium intake can have an effect, stronger in hypertensive individuals, blacks and older adults⁴²⁰ (LR: I, LE: A). Restricting sodium intake to about 1800 mg/day is associated with a 5.4 mm Hg decrease in SBP for hypertensive individuals⁴²¹ (LR: I, LE: A). Examples of sodium-rich foods include processed meats (ham, bologna, sausages, salami), bacon, dried meat, chicken nuggets; canned food (tomato extract, corn, peas), cheese (yellow cheese: Parmesan, provolone, prato), ready-made seasonings (Arisco®, Sazon®, soy sauce [shoyu], Worcestershire sauce, ketchup, mustard, mayo, concentrated extracts, meat tenderizers, and instant soup) and industrialized snacks (potato chips, French fries, and other snacks).⁴²² One part of salt restriction diets is to read the nutrition facts labels on all foods and choose those lower on salt (sodium chloride) and other sources of sodium, giving preference to fresh, frozen or “no salt added” canned vegetables, and to use herbs, spices, and saltless mixes to cook and season food. One should cook rice, pasta, and cereals without salt and choose items with low sodium content, deprecating frozen foods, pizza, ready-made mixes, canned soups and creams, and salad dressings. Whenever possible, wash off canned foods, such as tuna, to lower sodium intake. Some forms of salt (pink Himalayan salt and sea salt, among others) have the same sodium chloride content as table salt and rock salt.

8.5. Potassium

High-sodium diets are usually low on potassium, associated with higher incidence of HT. Several randomized controlled trials in population clusters have tested replacing sodium chloride table salt with low-sodium, high-potassium salt products, and led to decreases in BP⁴²³⁻⁴²⁸ (LR: I, LE: A). The magnitude of the effect on blood pressure varies with dietary sodium intake and the extent of its replacement by alternative sources of food in the population. A prior meta-analysis⁴²⁸ (LR: I, LE: A) confirmed the effect of sodium replacement for younger and older adults in the short and long term, though the hypotensive effect seems to be more pronounced for hypertensive individuals, with a mean difference of -8.87 mm Hg (95% CI: -11.19 to -6.55) in SBP and -4.04 mm Hg (95% CI: -5.70 to -2.39) in diastolic BP (DBP) over the control group⁴² (LR: I, LE: A). A meta-analysis of sodium restriction interventions found that, in six high-quality studies, ranging from two months to three years, salt substitutes (potassium chloride replacing sodium chloride from 25 to 50%) significant lowered SBP (-5.7 mm Hg; 95% CI -8.5 to -2.8) and DBP (-2.0 mm Hg; 95% CI -3.5 to -0.4) in China⁴²⁹ (LR: I, LE: A).

Potassium-rich foods include apricot, avocado, melon, skim milk, leafy greens, fish (flounder and tuna), beans, orange, peas, prune, spinach, tomato, and raisins.

8.6. Dairy Products

Dairy consists of a heterogeneous food group, and its impact on health should be assessed in terms of all of its components. Though rich in saturated fatty acids (in whole milk), they may contain potentially beneficial elements, such as whey protein, phospholipids from the fat globule membrane, calcium, magnesium, potassium, probiotics, and vitamins K₁ and K₂^{430,431} (LR: IIa, LE: B). Cohort studies suggest dairy consumption is inversely associated with CV risk disease^{432,433} (LR: IIa, LE: B). Some randomized controlled trials suggest a modest hypotensive effect, especially for nonfat dairy product^{434,435} (LR: IIa, LE: A) and milk proteins⁴³⁶ (LR: IIa, LE: B). Keep in mind that dietary guidelines recommend the consumption of low-fat dairy products^{437,438} (LR: IIa, LE: B).

8.7. Chocolate and Cocoa Products

A meta-analysis of ten randomized controlled trials (n = 297) found a 4.5 mm Hg decrease (95% CI: 3.3 to 5.9) and a 2.5 mm Hg decrease (95% CI: 1.2 to 3.9) in systolic and diastolic blood pressure, respectively, from increase consumption of cocoa products. The studies were very heterogeneous and the interventions, diverse⁴³⁹ (LR: IIa, LE: A). A recent meta-analysis found similar but weaker results⁴⁴⁰ (LR: IIa, LE: A). Two aspects deserve attention, though the more recent meta-analysis had more studies. One was that heterogeneity persisted across trials with variable amounts of flavonoids. The second is that increased intake of chocolate or cocoa products adds calories to the diet, which must then be set off by some degree of dietary restriction.

8.8. Coffee and Caffeinated Products

In addition to caffeine (Chart 8.2), coffee is also rich in bioactive compounds, such as polyphenols, especially chlorogenic acids, magnesium, and potassium, which may favor lower BP.⁴⁴¹ Caffeine can cause sharp increases in BP for over three hours, but regular consumption leads to tolerance.⁴⁴² Long-term coffee intake has not been associated with higher incidence rates of HT.⁴⁴³ On the contrary, meta-analyses of cohort studies show that coffee intake is associated with a mild decrease in hypertension risk^{443,444} (LR: IIb, LE: B). In the absence of robust experimental evidence, it is recommended that coffee intake should not exceed low to moderate amounts (≤ 200 mg of caffeine) (LR: IIa, LE: B).

8.9. Vitamin D

Despite some observational studies suggesting vitamin D deficiency being associated with higher blood pressure or higher incidence rates of hypertension^{445,446} (LR: IIb, LE: A), studies on vitamin D supplementation have found inconsistent results⁴⁴⁷⁻⁴⁴⁹ (LR: IIb, LE: A). Therefore, the role of vitamin D in blood pressure control is still unclear.

8.10. Supplements and Substitutes

In addition to lowering sodium intake from processed foods, other alternatives enable us to minimize the harmful effects from sodium consumption and, at the same time, enjoy the beneficial effects of potassium. In a randomized controlled trial, Chinese participants with prior cardiovascular disease or SBP above 160 mm Hg were selected at random to receive a combination of 65% sodium chloride, 25% potassium chloride, and 10% magnesium sulfate or 100%-sodium chloride table salt. The intervention resulted in a mean decrease of 3.7 mm Hg (1.6 to 5.9) in systolic pressure, with maximum effect in 12 months, a 5.4 mm Hg (2.3 to 8.5) decrease⁴²⁶ (LR: IIa, LE: B). A randomized controlled trial with hypertensive individuals and their families found similar but weaker results after 36 months²⁸ (LR: I, LE: A).

Though calcium supplementation may have a mild effect on preventing hypertension⁴⁵⁰ (LR: IIa, LE: B), its role in treatment has not yet been established. A meta-analysis of 12 randomized controlled trials found the use of multivitamin and multimineral supplements lowered BP in individuals suffering from chronic diseases. In a subgroup consisting of 58 hypertensive individuals, the analysis found a 7.98 mm Hg (14.95 to 1.02) decrease in SBP, but negligible significance for its impact on DBP⁴⁵¹ (LR: IIa, LE: B).

8.11. Weight Loss

The hypertensive effect of weight gain is well known. The relationship between BP and obesity rates is practically linear. Excess body fat, especially visceral fat, is a major risk factor for increased BP, which may be responsible for 65 to 75% of cases of HT.⁴⁵² Weight loss lowers BP even without reaching the desired weight. In a meta-analysis of 25 studies, losing 5.1 kg in weight led to a mean decrease of 4.4 mm Hg in SBP and 3.6 mm Hg in DBP⁴⁵³ (LR: I, LE: A). For overweight and obese individuals, weight loss is always an essential recommendation in HT treatment. Body fat assessments should not limit themselves to body mass index (BMI), but rather include central adiposity parameters, such as waist circumference (WC). Ideally, individuals should attain and maintain a healthy body weight, defined as BMI (kg/m²) < 25 in adults (LR: I, LE: A) and, according to the Brazilian Ministry of Health, from 22 to < 27 in older adults, as well as WC (cm) < 90 for men and < 80 for women. Evidence from a meta-analysis including participants from four continents shows that, for every 5-unit increases in BMI above > 25, the risk of early death increases approximately 31%, as does the 49% risk of cardiovascular mortality⁴⁵⁴ (LR: IIa, LE: B).

8.12. Alcohol Consumption

There is a linear relationship between alcohol consumption and BP, and alcohol abuse is linked to higher rates of HT. A recent meta-analysis, including 36 randomized controlled trials and 2865 participants, found that, for up to two drinks a day, lowering alcohol intake was not associated with significant decreases in BP. However, for individuals who took more than two drinks a day, lowering alcohol intake was associated with a greater decrease in BP, approximately 5.5 mm Hg (6.70 to 4.30) in SBP and 3.97 (4.70 to 3.25) in DBP. The decrease

was more pronounced for those who drank six or more drinks a day and lowered their intake by approximately 50%¹⁵ (LR: IIa, LE: B). Among drinkers, intake should not exceed 30 g of alcohol/day, ie, 1 bottle of beer (5% alcohol, 600 mL), two glasses of wine (12% alcohol, 250 mL), or one 1 dose (42% alcohol, 60 mL) of distilled beverages (whiskey, vodka, spirits). That threshold should be cut in half for low-weight men, women, the overweight, and/or those with high triglycerides. Teetotalers should not be encouraged to drink alcohol.¹⁵

8.13. Physical Activity and Physical Exercise

Physical activity (PA) refers to any body motion that increases energy expenditure above consumption at rest, such as walking, working, housework, and leisure activities. Physical exercise (PE), in turn, refers to structured, organized, and purposeful PA, with goals like improving health and/or fitness.⁴⁵⁵ Sedentary behavior is spent in low energy expenditure activities (≤ 1.5 MET), such as those performed sitting, reclining, or lying down (watching TV, sitting at the computer, playing video games, or working).⁴⁵⁶ Decreasing sedentary time, even for small periods, lowers the mortality risk⁴⁵⁷ (LR: IIb, LE: B).

Regular physical exercise lowers the incidence of HT.⁴⁵⁸ In addition, hypertensives who follow PA health recommendations show a 27 to 50% decrease in mortality risk, but lower levels of PA also produce benefits⁵³ (LR: I, LE: A). In HT treatment, additional benefits may be obtained from structure PE, with aerobic training supplemented by resistance training. Aerobic training has a proven effect in lowering office and ambulatory BP, while dynamic resistance training and isometric handgrip resistance training lower office BP, but there is no evidence that it lowers ambulatory BP.⁴⁵⁹ Chart 8.3 shows the magnitude of the effect of that training (LR: I, LE: A).⁴⁵⁹⁻⁴⁶¹

Other forms of training, such as aquatic exercise,⁴⁶² yoga,⁴⁶³ tai chi,⁴⁶⁴ and high-intensity interval training,⁴⁶⁵ among others, also seem to lower office BP for hypertensive patients. However, there is no documented evidence on their effects on ambulatory blood pressure nor on their potential risks, so they are still not recommended. Chart 8.4 lists physical activity and physical exercise recommendations.

Light to moderate PA and PE may be prescribed to for individuals without heart, cerebrovascular, or renal disease without prior medical assessment. If symptoms appear during PA or PE, it should be interrupted and the individual should seek medical help. Hypertensive individuals with comorbidities, who are symptomatic or who intend to participate in high-intensity or competitive activities should undergo a prior medical evaluation.⁴⁶⁶ The exercise stress test is recommended to evaluate physical fitness and to prescribe physical exercise,⁴⁶⁷ enabling an assessment of BP response to physical effort and check for coronary disease in symptomatic individuals or those with multiple risk factors. Training sessions should be canceled if BP is above 160/105 mm Hg; measuring BP during aerobic training is recommended for hypertensive individuals who exhibit hyper-reactivity, and the intensity of the physical activity should be lowered if BP is above 180/105 mm Hg (LR: IIa, LE: C).

8.14. Slow Breathing

Slow or guided breathing requires respiratory rate reduction to 6-10 breaths/minute for 15-20 minutes/day to promote casual BP reduction. Randomized controlled trials on device guided breathing (Resperate device®), analyzed in a previous meta-analysis, found no significant decrease in BP after excluding five studies involving industry participation.⁴⁶⁸ A recent meta-analysis, combining six voluntary slow breathing exercise trials compared to natural breathing, found a 6.36 mm Hg decrease in SBP (95% CI: 10.32 to 2.39) and a 6.39 mm Hg decrease in DBP (95% CI: 7.30 to 5.49) in DBP compared to control group participants in randomized controlled trials lasting up to six months.⁴⁶⁹ Existing evidence shows that, in the short run, voluntary slow breathing exercises can lower SBP and DBP in HT patients with CV disease (LR: IIa, LE: A). In a clinical trial with a small number of participants, slow breathing was shown to lower blood pressure at rest for individuals with isolated HT, in addition to responses to static and dynamic exercises⁴⁷⁰ (LR: IIb, LE: B).

The association between listening to music and deep breathing, in comparison with listening to music only, did not result in statistically significant BP reductions. Participants from both treatment groups achieved clinically significant BP reductions⁴⁷¹ (LR: IIb, LE: B).

8.15. Stress Control

Overall, no robust evidence on the efficacy of techniques used in stress management has been found, including behavioral therapies, transcendental meditation (LR: IIb, LE: B), other meditation techniques (LR: III, LE: C), yoga (LR: III, LE: C), relaxation therapies (LR: III, LE: C), and biofeedback approaches (LR: IIb, LE: B). There is more evidence for guided slow breathing than there is available for acupuncture (LR: III, LE: B). Clinical indications show only a trend towards lowering BP, whether used separately or in combination⁴⁷² (LR: IIa, LE: B). In two meta-analyses, music therapy was associated with a significant reduction in SBP^{473,474} while in a third only its tendency to lower BP was observed⁴⁷⁵ (LR: IIb, LE: A).

Meditation can be seen as the experience of emptying one's mind and making it devoid of thought; the practice of focusing one's concentration on a single object until becoming aware of that object; contemplating a single aspect of reality; or developing a given mental or even behavioral quality.^{476,477} A systematic review showed that transcendental meditation led to a 4 mm Hg decrease in SBP and a 2 mm Hg decrease in DBP⁴⁷⁸ (LR: IIb, LE: B). However, the mechanisms through which meditation lowers BP are not

fully understood, and others have criticized these studies for methodological limitations.⁴⁷⁹

8.16. Religiosity and Spirituality

Spirituality is associated with physical, psychological and social aspects, enabling a more holistic view of human beings and placing them at the center of attention and of treatment⁴⁸⁰ (LR: IIb, LE: C). It may be considered a set of moral, mental and emotional values that guide thoughts, behaviors, and attitudes^{3,481} (LR: I, LE: B). Religion, in turn, is understood as an organized system of beliefs, practices, and symbols with the purpose of bringing its adherents closer to the transcendental or the divine^{3,481} (LR: I, LE: B).

Studies suggest there is an association between religiosity and spirituality (R/S) and all-cause mortality, cancer, and CV mortality, as well as quality of life⁴⁸²⁻⁴⁸⁵ (LR: I, LE: B). The relevant mechanisms involve favorable changes in lifestyle and CVRFs, such as lower levels of serum glucose, cholesterol, fibrinogen, cortisol, and inflammatory cytokines^{481,486} (LR: I, LE: B).

Given the multidimensional aspects of R/S and the characteristics of study populations, observational studies that assess the association between BP and/or HT risk have found heterogeneous results, but most suggest beneficial effects.^{77,481,487,488} In the SWAN (Study of Women's Health Across the Nation) study, with over 1600 middle-aged women as participants, daily spiritual practices were not found to be protective for SBP or HT.⁴⁸⁹ In the Chicago Community Adult Health Study, frequency of religious attendance was not associated with HT, while the habit of prayer had a positive association. Spirituality was connected to diastolic HT, while the meaning of forgiveness was associated with lower DBP and lower probability of HT.⁴⁹⁰ In a different study, more frequent religious attendance was associated with lower DBP, but not lower SBP⁴⁹¹ (LR: IIa, LE: B).

A recent review found that elements of R/S may interfere positively in adherence to pharmacological treatment, but other studies have found opposite or mixed effects, especially for severe and chronic diseases⁴⁹² (LR: IIa, LE: C). Health care professionals should learn to identify patient demands and expectations, provide adequate support, and overcome conflicts. Open-ended questions or semistructured surveys can be useful to that end^{3,493} (LR: I, LE: B). Despite the fact that evidence from observational studies correlate R/S and HT, few clinical trials have assessed the effects of interventions in this area, especially for severe CV diseases, chronic diseases or palliative care^{481,494} (LR: IIb, LE: B).

Key Takeaways

Hypertensive individuals should be assessed in terms of smoking habits, and smoking cessation should be pursued, with the help of medications if needed, since it increases CV risk.

Diets like DASH, which increase fruit, vegetable, low-fat dairy, and whole-grain intake as well fostering moderate consumption of nuts and lower fat, candy, sugary beverages, and red meat consumption, should be prescribed

Daily sodium intake should be restricted to 2 g/day, with sodium chloride replaced by potassium chloride where there are no restrictions.

Body weight should be controlled to maintain BMI < 25 kg/m².

Individuals should perform at least 150 minutes of moderate physical activity per week Decreasing sedentary behavior should be encouraged, with individuals standing for 5 minutes for every 30 minutes spent sitting down.

Chart 8.1 – Example of food portions and quantities recommended in DASH diet for daily or weekly intake for individuals consuming 2000 kcal/day

Food group	Daily portions	Portion size/unit
Fruit	4-5	1 medium fruit 1/4 cup of dried fruit 1/2 cup fresh, frozen, or canned fruit 177 mL fruit juice
Vegetables	4-5	1 cup raw leafy green vegetable 1/2 cup of cooked vegetables 177 mL vegetable juice
Diet dairy products	2-3	237 mL milk 1 cup of yogurt 42 g cheese
Grains and derivatives**	7-8	1 slice of bread 1 cup of ready-to-eat cereal* 1/2 cup cooked cereal, rice, or pasta
Lean meat, poultry, and fish	≤ 2	85 g cooked lean meat, skinless poultry, or fish
Nuts, seeds and legumes***	4-5 times a week	1/3 cup or 42 g nuts 1 tablespoon or 14 g seeds 1/2 cup of cooked dried beans

* Portion sizes range from 1/2 cup to 1 1/4 cup. ** Corn, oat, granola, whole rice. *** Cashew nut, Brazil nut, almonds, peanuts, beans, lentils. Adapted from Fuchs, 2001.⁴²²

Chart 8.2 – Caffeine content of caffeinated beverages

	Volume (mL)	Caffeine (mg)
Drip coffee	355	235
Instant coffee	237	63
Espresso	30	63
Decaf	237	2
Black tea	237	47
Green tea	237	28
Cammomile tea	237	0

Adapted from van Dam RM, Hu FB, Willett WC, 2020.⁴⁴²

Chart 8.3 – Magnitude of blood pressure reduction in hypertensive individuals with physical training

Training	Systolic/diastolic blood pressure
Aerobic ⁴⁵⁹	-12.3/-6.1 mm Hg*
Aerobic ⁴⁵⁹	-8.8/-4.9 mm Hg**
Dynamic resistance training ⁴⁶⁰	-5.7/-5.2 mm Hg
Isometric handgrip resistance training ⁴⁶¹	-6.5/-5.5 mm Hg

* Office blood pressure. ** Ambulatory blood pressure monitoring.

Guidelines

Chart 8.4 – Physical activity and physical exercise recommendations.

Recommendations

Decrease sedentary behavior – LR: IIb, LE: B

Stand for 5 minutes for every 30 minutes sitting down.

Recommended physical activity at population level – LR: I, LE: A

Perform at least 150 minutes of moderate physical activity per week

Physical training – aerobics supplemented with resistance training – LR: I, LE: A

Prescription of aerobic training – mandatory

Various modalities: walking, running, dancing and swimming, among others.

Frequency: 3 to 5 times per week (more often is better)

Duration: 30 to 60 minutes per session (longer is better)

Moderate intensity defined by:

1) Highest intensity still able to have a conversation (without panting)

2) Feeling “slightly tired” to “tired” (11 to 13 in the Borg scale)

3) Keep heart rate (HR) during training in the following range:

$HR_{\text{training}} = (HR_{\text{max}} - HR_{\text{rest}}) \times \% + HR_{\text{rest}}$

Where:

HR_{max}: obtained either on a maximum exercise test, using the regular medications, or by calculating maximum HR estimated for age ($220 - \text{age}$). The formula may not be used with hypertensive patients suffering from heart disease, taking beta-blockers or taking dihydropyridine calcium channel blockers.

HR_{rest}: measured after 5-minute rest lying down.

%: use 40% as lower threshold and 60% as upper threshold.

Prescription of endurance training – complementary

2 to 3 times a week

8 to 10 exercises for the major muscle groups, prioritizing unilateral execution, when possible

1 to 3 sets

10 to 15 repetitions up to moderate fatigue (repetition with decreased motion speed) – approximately 60% of 1RM

Long passive pauses – 90 to 120 s

9. Pharmacological Treatment

9.1. Treatment Objectives

Cardiovascular (CV) protection is the primary objective of antihypertensive treatment. Lower blood pressure (BP) is the first goal, while the greater objective is to reduce the CV outcomes and mortality linked to hypertension (HT).^{5,37,164,495} Meta-analyses of randomized clinical trials studying hypertensive patients show that decreasing systolic BP by 10 mm Hg and diastolic BP by 5 mm Hg with medications is accompanied by a significant decrease in relative risk for major outcomes: 37% for risk of stroke, 22% for coronary artery disease (CAD), 46% for heart failure (HF), 20% for CV mortality, and 12% for all-cause mortality.^{83,85,307,308,496,497} The higher the CV risk, the greater the benefits, but there are benefits even for patients with small BP elevations and low to moderate CV risk.^{307,308,496}

It should be stressed that these findings come mostly from clinical trials involving high CV risk hypertensives age 50 and older, and follow-up is rarely longer than five years. Therefore, the benefits for young individuals, for low- to moderate-risk individuals, and from longer treatment periods are extrapolated from the scientific evidence available.⁴⁹⁸ In particular, for this patient group, we infer that assessing the impact of antihypertensive medications in protecting end-organs may be a useful indirect indicator for treatment effectiveness, especially reduction of left ventricular mass^{499,500} and albuminuria.⁵⁰¹ Thus, adequate treatment for individuals below the age of 50 is strongly recommended.

9.2. General Principles of Pharmacological Treatment

Most hypertensive patients require medications in addition to lifestyle changes in order to achieve their blood-pressure targets.^{5,37,83,164,307,308,495,497,502} Chart 9.1 shows the recommended treatment onset for lifestyle interventions and pharmacological treatment according to blood pressure, age, and cardiovascular risk.

The five main classes of antihypertensive medication—diuretics (DIUs), calcium channel blockers (CCBs), angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), and beta-blockers (BBs)—have shown to significantly lower BP compared to placebos, as well as produce significant decreases in fatal and nonfatal CV outcomes, and this benefit is fundamentally linked to the BP decrease.^{5,37,83,164,307,308,495,497} BBs are useful in specific clinical conditions: post-acute myocardial infarction (AMI), chest angina, HF with reduced ejection fraction (HFrEF), heart rate (HR) control, and women of childbearing age.^{5,37,164,495} Other classes, such as alpha-blockers, centrally acting sympatholytics, aldosterone antagonists and direct vasodilators, have not been as widely studied in clinical trials, are associated with higher rates of adverse events, and should only be used when BP control has not been achieved with combinations based on the primary medication classes mentioned above.^{37,164,495,503,504}

The desirable features of antihypertensive medications are that they:

- Have shown the ability to reduce CV morbidity and mortality;

- Be effective orally;
- Be well tolerated;
- Preferably be administered in a single daily dose;
- Able of being used in association;
- Have quality control in its production.

Additional recommendations are:

- Use for at least four weeks, before any change, except for special situations;
- Do not use compound medications, which are not subject to pharmacokinetic control and pharmacovigilance;
- Patients are instructed about the importance of continuous use of antihypertensive medication, the occasional need for dose adjustments and switching or combination of drugs, and the occasional onset of adverse effects;
- There is no sufficient evidence for recommending routine nocturnal administration of antihypertensive medications, except under special conditions.

9.3. Therapy Regimens

Pharmacological treatment may start as monotherapy or as drug combinations. It should be emphasized that the use of drug combinations is the preferred strategy for most hypertensive patients (Figure 9.1).

9.3.1. Monotherapy

Monotherapy can be the initial antihypertensive strategy for stage 1 HT patients at low CV risk^{37,164,495}, with BP 130-139/85-89 mm Hg at high CV risk³⁰⁷ or older adults and/or frail individuals⁴ (Figure 9.1). For these patient profiles, the desired BP decrease is small and should be achieved gradually in order to prevent adverse events.^{37,164,495,502}

Treatment should be individualized, and the initial choice of medication should be based on the general desirable characteristics of the antihypertensive medications described previously, on individuals particularities, on the presence of associated diseases and end-organ damage (EOD), and on socioeconomic conditions.^{5,37,164,495}

The preferred classes of antihypertensive medication^{5,37,164,495} for BP control in the initial monotherapy are as follows:

- Thiazide and thiazide-like diuretics,^{83,307,497}
- CCBs,^{83,307,497}
- ACEIs,^{83,307,497}
- ARBs.^{83,307,497}

BBs may be considered as the initial drug in certain situations,^{5,37,83,164,307,495,497} as described above, and are more frequently used in combination with other medications. Dosages may be adjusted in order to achieve recommended blood-pressure targets.

9.3.2. Drug Combinations

Drug combination are the preferred therapeutic strategy for most hypertensive patients, regardless of HT staging and associated CV risk^{5,37,164,495,502-507} (Figure 9.1). Treatment should begin with a combination of two medications with different

mechanisms of actions, except for the association of thiazide DIUs and potassium-sparing DIUs. If the blood-pressure target is not reached, adjusting doses and/or adding a third drug are indicated. Next, more medications are added until the BP control is achieved.⁵⁰²⁻⁵⁰⁴

The rationale for drug combinations is based on the incremental antihypertensive effect when working on different physiopathological mechanisms by synergistic actions and by inhibiting the activation of counter-regulatory mechanisms.^{502,503} In addition, drug combinations have the potential of decreasing the rate of side effects due to the lower dose of each combined medication or the ability of one drug to antagonize the adverse effects of another.^{502,503} Higher adherence to treatment and decreased therapeutic inertia are important benefits. Fixed-dose and single-pill combinations are preferable, as they are associated with higher adherence to treatment and, consequently, to better clinical results.^{502,503}

The onset of fixed-dose drug combination treatment is associated with decreased risk of CV outcomes compared to the traditional onset of treatment with monotherapy, faster achievement of blood-pressure targets, protection of end-organs, and long-term CV outcomes.⁵⁰²⁻⁵⁰⁷

9.4. General Characteristics of Different Classes of Antihypertensive Medications

Chart 9.2 lists the antihypertensive medications available in Brazil, divided by therapeutic class.

9.4.1. Diuretics (DIUs)

The mechanisms of antihypertensive action of DIUs are initially related to their natriuretic effects, with a decrease in the circulating volume and extracellular volume. After 4-6 weeks, circulating volume normalizes and a reduction in peripheral vascular resistance (PVR) occurs. Diuretics lower BP and CV morbidity and mortality.⁵⁰⁸⁻⁵¹⁰ Their antihypertensive effect is not directly related to their doses, but side effects are associated with dose and potency of diuretic action. Thiazide (hydrochlorothiazide) or thiazide-like (chlorthalidone and indapamide) DIUs at low doses should be preferred, because they are milder and longer-acting. Loop DIUs (furosemide and bumetanide) should be reserved for clinical conditions featuring sodium and fluid retention, such as renal failure (creatinine > 2.0 mg/dL or estimated glomerular filtration rate ≤ 30 mL/min/1.73m²) and edema (HF or nephritic syndrome). Potassium-sparing DIUs (spironolactone and amiloride) are usually associated with a thiazide or loop DIU. Spironolactone is habitually used as the fourth medication in drug combinations for patients with resistant and refractory HT. This aspect is discussed in further detail in the chapter 16 to those more severe forms of HT.

Chlorthalidone has higher diuretic potency than hydrochlorothiazide, compared at proper doses, and its longer half-life made it the preferential DIU for resistant or refractory HT, since sodium and fluid retention is an important mechanism in resistance to treatment.⁵⁰⁴ The indication of chlorthalidone as the preferred DIU because it promotes a higher decrease in CV events is controversial, as a meta-analysis and observational studies with large

numbers of participants were not in agreement.^{495,511,512} On the other hand, as expected from the more intense diuretic effect, these studies have found greater rates of adverse effects for chlorthalidone, particularly hydroelectrolytic and metabolic disorders. Indapamide, a thiazide-like, which has been growing in use in recent years, like chlorthalidone, has greater potency and longer-acting diuretic effect; like previous medications, it has proven antihypertensive effect, decreases CV events and has a positive metabolic profile.⁵¹³ Thus, there is no definitive data behind the preference for chlorthalidone in antihypertensive treatment for individuals with normal renal function, but it may be used when a larger diuretic effect is desirable, especially in resistant HT, as it is more potent than hydrochlorothiazide.

9.4.1.1. Adverse Effects of Diuretics

Major adverse effects of diuretics are weakness, cramps, hypovolemia, and erectile dysfunction. Hypopotassemia is the most common metabolic effect, often accompanied by hypomagnesemia, which can induce ventricular arrhythmias, mainly extrasystole. Hypopotassemia also leads to insulin secretion, increasing glucose intolerance, and the risk of developing type 2 diabetes mellitus. Uric acid increase is an almost universal effect of DIUs, and may trigger gout crises in predisposed individuals.

The use of low doses of DIUs decreases the risk of adverse effects without hindering their antihypertensive efficacy, especially when associated with other drug classes. Spironolactone may cause gynecomastia and hyperpotassemia, and the latter is the most frequent electrolyte disorder in patients with impaired renal function. There are reports that indapamide may have a better metabolic profile than hydrochlorothiazide.⁵¹³

9.4.2. Calcium Channel Blockers (CCBs)

This medication class blocks the calcium channels in smooth muscle cell membranes in the arterioles, lowers calcium availability inside cells to impair muscle contraction, and consequently decreases peripheral vascular resistance by vasodilation.^{514,515}

CCBs can be divided into two basic forms: dihydropyridines and nondihydropyridines. Dihydropyridines (amlodipine, nifedipine, felodipine, manidipine, levamlodipine, lercanidipine, lacidipine) are predominant vasodilators, with minimum interference in HR and systolic function, and therefore are more often used as antihypertensive agents.

Nondihydropyridines, such as diphenylalkylamines (verapamil) and benzothiazepines (diltiazem), have a lower vasodilating effect, and act on the heart musculature and the cardiac conduction system. Thus, they lower HR, have an antiarrhythmic effect and can depress systolic function, primarily in patients already suffering from myocardial dysfunction, and should be avoided in individuals with that condition.

Long-acting CCBs should be preferred to prevent unwanted oscillations in HR and BP. They are effective antihypertensive medications that reduce CV morbidity and mortality.^{307,515-517} An outcome study has reaffirmed the efficacy, tolerability

and safety of this drug class HT treatment in CAD patients,⁵¹⁸ making it an alternative to BBs when the latter cannot be used, or in combination for cases of refractory angina.

9.4.2.1. Adverse Effects of Calcium Channel Blockers

Ankle swelling is usually the most common side effect, resulting from the vasodilating action (more arterial than venous), which causes capillary transudation. Throbbing headaches and dizziness are common. Facial blushing is more common with fast-acting dihydropyridine CCBs. Hyperchromia of the distal third of the legs (ochre dermatitis) and gingival hypertrophy are two occasional adverse effects.

Adverse effects are usually dose-dependent, may cause intolerance to dihydropyridine CCBs and may result in resistance to treatment. In these cases, lipophilic CCBs (manidipine, lercanidipine, lacidipine) may be tested, or levamlodipine at low doses. Verapamil and diltiazem can worsen HF, as well as bradycardia and atrioventricular block. Verapamil has been found to cause constipation.⁵¹⁶

9.4.3. Angiotensin-Converting Enzyme Inhibitors (ACEIs)

Angiotensin-converting enzyme inhibitors are effective antihypertensive drugs whose primary action is inhibiting angiotensin I converting enzyme, responsible for both transforming angiotensin I into angiotensin II (vasoconstrictor) and lowering bradykinin degradation (vasodilator). They are effective for HT treatment, lowering CV morbidity and mortality.³⁰⁷ They have been shown to be useful in many other CV conditions, such as HFrEF and post-AMI anti-remodeling, and may have antiatherosclerotic properties. They also delay renal function decline in patients with diabetic nephropathy or kidney diseases of other etiologies, especially in case of albuminuria.⁵¹⁹

9.4.3.1. Adverse Effects of Angiotensin-Converting Enzyme Inhibitors

Usually well-tolerated by most hypertensive patients, its major side effect is dry coughs, affecting 5 to 20% of patients. Angioneurotic edema and skin rashes are rare.⁵²⁰ When administered to renal failure patients, it can initially worsen renal function, usually discretely, due to adjustments in intraglomerular hemodynamics (vasodilation of efferent arterioles and lower glomerular filtration pressure) resulting in higher plasma creatinine and urea rates.⁵²¹ However, the initial loss of renal function is a protective mechanism, since it prevents glomerular hyperfiltration and slows down the progression of chronic kidney disease.⁵²² In case of major loss of renal function (> 30%), the medication should be withdrawn and the possibility of bilateral renal artery stenosis or renal artery stenosis in solitary functioning kidney.

ACEIs and other renin-angiotensin-aldosterone system (RAAS) blockers may cause hyperkalemia in patients with renal failure, especially diabetic patients, and are contraindicated during pregnancy due to the risk of fetal complications.^{523,524} Therefore, they should be carefully monitored when administered to adolescents and women of childbearing age.

9.4.4. Angiotensin II AT1 Receptor Blockers (ARBs)

ARBs antagonize angiotensin II action via the specific blockade of AT1 receptors, responsible for the primary effects of angiotensin II (vasoconstriction, cell proliferation and aldosterone release). In HT treatment, especially in populations at high CV risk or with comorbidities, they decrease CV and renal (diabetic nephropathy) morbidity and mortality.⁵²⁵⁻⁵³¹

9.4.4.1. Adverse Effects of Angiotensin II AT1 Receptor Blockers

Adverse effects related to ARBs are not common, with exanthema observed in rare occasions. Like ACEIs, ARBs may promote an initial decrease in glomerular filtration via vasodilation of efferent arterioles, lowering glomerular filtration pressure, but the effect is nephroprotective in the long run.⁵²⁹⁻⁵³¹ Similarly to ACEIs, ARBs may cause hypercalcemia, especially in the presence of renal failure, and are contraindicated during pregnancy, and the same care should be taken for women of childbearing age.

9.4.5. Beta-Blockers (BBs)

Beta-blockers have complex pharmacological actions. They promote an initial decrease in cardiac output and renin secretion, with readaptation of baroreceptors and decrease in catecholamines in nervous synapses.^{532,533}

They can be divided into three categories, according to selectivity in adrenergic receptor binding: 1) nonselective: block both beta-1 adrenergic receptors, found mainly in the myocardium, and beta-2 receptors, found in smooth muscle, the lungs, blood vessels and other organs (propranolol, nadolol and pindolol, the latter displaying intrinsic sympathomimetic activity, acting as a partial adrenergic agonist and producing less bradycardia); 2) cardioselective: preferentially block beta-1 adrenergic receptors (atenolol, metoprolol, bisoprolol and nebivolol, which is the most cardioselective); and 3) vasodilator: manifests as peripheral alpha-1 adrenergic receptor antagonism (carvedilol) and nitric oxide production (nebivolol).⁵³²⁻⁵³⁵ Propranolol is useful to patients with essential tremor, mitral valve prolapse, hyperkinetic syndromes (hyperthyroidism and panic disorder), vascular headache, and portal hypertension.^{532,533}

A meta-analysis⁵³⁶ including over 130 thousand primary hypertension patients compared BBs to other classes of antihypertensive medications, placebos, and no treatment. It found that compared to other antihypertensive medications (DIUs, CCBs, ACEIs, ARBs), beta-blockers increase the risk of stroke by 16%. Compared to placebo or untreated patients, beta-blockers the lower risk of stroke, but only half as much as would be expected from observed blood pressure decreases. The meta-analysis⁵³⁴ also found that compared to other antihypertensive medications, atenolol increases the risk of stroke by 26% and overall mortality by 8%, both significant results. This is the main reason this guideline recommends BBs as an initial antihypertensive medication only in cases for which there is a specific indication.

9.4.5.1. Adverse Effects of Beta-Blockers

The adverse effects are bronchospasm, bradycardia, atrioventricular conduction disorders, peripheral vasoconstriction, insomnia, nightmares, depression, asthenia, and sexual dysfunction. BBs are contraindicated for patients with asthma, chronic obstructive pulmonary disease (COPD), and second- and third-degree atrioventricular block. They may lead to glucose intolerance, induce onset of diabetes mellitus, hypertriglyceridemia, high LDL-cholesterol, and low HDL-cholesterol. The impact on glucose metabolism is potentiated when combined with DIUs. Third-generation BBs (carvedilol and nebivolol) have neutral impact or may even improve the glucose and lipid metabolism, possibly because of their vasodilatory effect, with decrease in insulin resistance and improvement of glucose uptake by peripheral tissues.^{532,535} Studies on nebivolol have also found less sexual dysfunction, possibly due to its effect on endothelial nitric oxide synthesis.^{532,535}

9.4.6. Centrally Acting Sympatholytics

Centrally acting alpha-agonists stimulate the alpha-2 receptors involved in sympatho-inhibitory mechanisms.⁵³⁷ Their well-defined effects are as follows: a decrease in sympathetic activity and baroreceptor reflex, contributing to relative bradycardia and orthostatic hypotension; mild decrease in PVR and cardiac output; lower plasma renin levels; and fluid retention. Representatives of that group include methyl dopa, clonidine, and the imidazoline receptor inhibitor rilmenidine.^{538,539} Clonidine also acts on presynaptic alpha-2 receptors, which prevent norepinephrine release. It accumulates in nerve endings and, when withdrawn suddenly, the uncontrolled release may cause an adrenergic crisis.⁵³⁷ Despite some central alpha-2 agonism, rilmenidine has greater affinity for subtype I imidazoline receptor binding sites, causing fewer undesirable effects than clonidine.⁵³⁸

This class of medication has no unwanted metabolic effects and do not interfere with peripheral resistance to insulin or to the lipid profile. Methyl dopa is primarily indicated for HT during pregnancy, as it is used for short periods, there is a large body of experience with its use during this period, and it has a better safety profile for pregnant women and for fetuses.^{537,539} Clonidine can be useful in HT associated with restless legs syndrome,⁵⁴⁰ opioid withdrawal,⁵⁴¹ menopausal hot flashes,⁵⁴² diarrhea associated with diabetic neuropathy,⁵⁴³ and sympathetic hyperactivity in patients with alcoholic cirrhosis.⁵⁴⁴

9.4.6.1. Adverse Effects of Centrally Acting Sympatholytics

Methyl dopa can cause autoimmune reactions, such as fever, hemolytic anemia, galactorrhea, and liver dysfunction, which, in most cases, disappear with cessation of use. If an adverse reaction occurs, methyl dopa can be replaced by another central alpha-agonist.⁵³⁹

There is a risk of rebound effect from the discontinuation of clonidine, especially when combined with beta-blockers, and can be dangerous in the preoperative period.⁵³⁷ Gradual withdrawal over two to four weeks prevents the rebound

effect. Medications in this class have adverse reactions due to their central action, such as drowsiness, sedation, dry mouth, fatigue, postural hypotension, and erectile dysfunction.^{537,539}

9.4.7. Alpha-blockers

Alpha-blockers act as competitive antagonists of postsynaptic alpha-1 receptors, decreasing PVR without changes in cardiac output.⁵³⁹ They promote greater blood pressure decreases in standing position and in reflex tachycardia. Therefore, postural hypotension is common, often found after the first dose. The hypotensive effect is mild in monotherapy, the combined use being preferred. They have favorable and discrete action on the lipid and glucose metabolisms.⁵³⁹ Medications in this class used as antihypertensives include doxazosin, prazosin, and terazosin.

A beneficial adjunct action of alpha-1 blockers is the relaxation of the pelvic floor musculature, which helps patients with benign prostatic hyperplasia (BPH) empty their bladders. Therefore, alpha-blockers are also used in men with BPH, particularly doxazosin, tamsulosin, alfuzosin, and silodosin.

9.4.7.1. Adverse Effects of Alpha-Blockers

Alpha-blockers may cause symptomatic hypotension on the first dose. Tolerance is a frequent phenomenon, requiring increasing doses to maintain the antihypertensive effect (tachyphylaxis). Alpha-blockers may cause urinary incontinence in women. There is evidence that patients treated with doxazosin are at higher risk for HF.⁵³⁹

9.4.8. Direct-Acting Vasodilators

The oral medications in this class are hydralazine and minoxidil. They act directly by relaxing arterial smooth muscles, leading to a PVR decrease.⁵³⁹

9.4.8.1. Adverse Effects of Direct-Acting Vasodilators

The side effects of hydralazine are headache, flushing, reflex tachycardia, and lupus-like reaction (dose-dependent).⁵³⁹ In addition, it can cause anorexia, nausea, vomiting, and diarrhea. Vasodilators may cause sodium and fluid retention, with increased circulating volume and reflex tachycardia. A side effect of minoxidil is hirsutism, found in approximately 80% of the patients.

9.4.9. Direct Renin Inhibitors

Aliskiren, the only representative of this drug class commercially available, causes direct renin inhibition with consequent decrease in angiotensin II production.⁵⁴⁵ Other actions may contribute to BP lowering and tissue protection, such as the reduction in plasma renin activity,⁵⁴⁵ renin/prorenin receptor blockade,⁵⁴⁶ and decrease in intracellular angiotensin II production.⁵⁴⁷

Antihypertensive efficacy studies have confirmed its antihypertensive activity in monotherapy and in combination, at a similar level as other RAAS blockers and with the apparent additional benefit of lowering proteinuria in kidney

disease patients.^{548,549} However, there is no evidence of its benefits on CV morbidity and mortality for hypertensive and prehypertensive patients.^{550,551}

9.4.9.1. Adverse Effects of Direct Renin Inhibitors

They are well tolerated. Skin rashes, diarrhea (especially at high doses above 300 mg/day), creatine phosphokinase increases, and coughing may occur in less than 1% of patients. They are contraindicated during pregnancy for the same reasons as ACEIs and ARBs.

9.5. Antihypertensive drug combinations

Initial antihypertensive drug combination therapy seems to be associated with decreased risk of CV outcomes compared to the traditional onset of treatment with monotherapy.⁵⁵² Initial two-drug combinations, compared to sequential association promotes quicker control and may lower BP up to five times more,⁵⁰⁶ with clear impact on EOD and long-term CV outcomes. A meta-analysis found that fixed-dose two-drug combinations improve adherence by 24% compared with a free-drug component regimen.⁵⁵³ However, few studies focus specifically on assessing drug combinations on CV outcomes.

The ACCOMPLISH study⁵⁵⁴ compared benazepril combined with hydrochlorothiazide and with amlodipine. The difference in systolic and diastolic BP between the two groups, though significant, was only 0.9/1.1 mm Hg lower in the amlodipine arm. There was a decrease in risk of primary outcomes, consisting of nonfatal AMI, stroke, hospitalization for unstable angina, myocardial revascularization surgery, and cardiopulmonary resuscitation, in favor of the benazepril-amlodipine group. The choice of hydrochlorothiazide in that study was criticized because its effect lasts less than 24 hours, unlike the longer-acting amlodipine. However, a different report found no significant differences in 24-hour BP across groups.⁵⁵⁵ In patients with body mass index (BMI) > 30 kg/m², there were no differences in primary outcomes between the two groups.⁵⁵⁶ Another prespecified analysis found an addition decrease in kidney disease progressions from a benazepril-amlodipine combination.⁵⁵⁷

The ASCOT-BPLA study⁵⁵⁸ compared a strategy based on amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide. Approximately 78% of patients in each group used combination therapy for hypertension control. There were no differences in primary outcomes, consisting of nonfatal AMI and fatal CAD, but secondary outcomes, such as stroke, fatal coronary events, CV mortality, and all-cause mortality, were all significantly lower for the amlodipine group. De novo diabetes development rates were 30% higher for the group treated with BBs and thiazide. The CAFE sub-study²³⁴ found a more significant decrease in central aortic pressure from an amlodipine-perindopril combination and attributed it, at least in part, to the greater decrease in secondary outcomes for the group.

In the multicenter VALUE trial,⁵²⁷ high CV risk patients received antihypertensive treatment based on valsartane or amlodipine. Approximately 25% of patients in both groups required the addition of 12 to 25 mg of hydrochlorothiazide for BP control. Despite the higher and earlier blood pressure

decrease in the amlodipine group, the combined primary cardiac outcome at the end of four years was similar for both groups, as were the fatal AMI and all-cause mortality rates. There were fewer HF cases with valsartane and fewer nonfatal AMI and stroke cases with amlodipine.

In HOPE-3,³⁰⁹ directed primarily to studying the effects of medications in prehypertensive patients at intermediate CV risk, an initial strategy based on a fixed-dose combination of candesartan and hydrochlorothiazide led to a 27% decrease in the composite outcome risk of CV death, nonfatal AMI, and stroke in stage 1 hypertension individuals. However, no benefits have been found for prehypertensives.

The PROGRESS trial,²⁹¹ which assessed patients with prior cerebrovascular disease; the ADVANCE trial,⁵⁵⁹ which studied individuals with type 2 diabetes; and HYVET,⁵⁶⁰ which studied patients 80 years of age or older, used an intervention based on perindopril and indapamide and showed the benefits of combining DIUs and ACEIs to lower issues such as stroke and vascular dysfunction; macro- and microvascular outcomes; and death, stroke, and HF, respectively.

Combining BBs and thiazides lowered CV outcomes when compared to a placebo in older trials, especially those involving older patients,^{509,561,562} but underperformed the combination of thiazides and losartan in the LIFE trial,⁵²⁶ where it provided less protection against stroke and favored glucose metabolic disorders. The use of fixed-dose combinations of thiazides with atenolol and other BBs should be restricted to specific indications for this class^{5,164,495} given the induction of potential metabolic disorders from DIUs, such as insulin resistance, hyperglycemia, hyperuricemia, and hypokalemia.

The combination of dihydropyridine calcium channel blockers and thiazide diuretics may be especially useful for older adults with isolated systolic hypertension or in cases where the use of RAAS blockers are contraindicated or restricted due to their potential risks, such as in women of childbearing age.

The polygon in Figure 9.2 shows the preferred (connected by a green line), contraindicated (red line) and possible but less often studied (dotted line) combinations.¹ In stage 3 hypertension and resistant hypertension patients, the goal is to optimize the triple treatment with preferred medications—ACEIs or ARBs, dihydropyridine CCBs, and thiazide or thiazide-like DIUs.^{37,503,504} A clinical trial assessed the fixed triple combination of amlodipine, valsartan, and hydrochlorothiazide, all available in Brazil, for stages 2 and 3 HT patients, and found mean decreases of 39.7 mm Hg in systolic BP and 24.7 mm Hg in diastolic BP, significantly higher than two-drug combinations involving the same medications.⁵⁶³

Failing to reach the blood-pressure target with triple therapy requires the use of a fourth drug, and the current preferred medication is spironolactone.^{37,564-567} BBs, clonidine,⁵⁶⁴ and doxazosin⁵⁶⁷ are options for 4th or 5th drugs, and hydralazine¹⁶⁴ may also be added in cases of intolerance to any of the previous antihypertensive options and in resistant HT.^{503,504} In the PATHWAY 2 study,⁵⁶⁷ amiloride use was shown to be as effective as spironolactone, providing an alternate treatment for resistant HT. However, the medication is not available from

Guidelines

manufacturers in Brazil. The ReHOT study⁵⁶⁴ showed that the efficacy of clonidine is similar to that of spironolactone as the 4th medication for resistant HT patients. However, in 24-hour ambulatory BP analysis, spironolactone outperformed clonidine.

Treatment combining two renin-angiotensin system blockers, such as an ACEI with an ARB or any of the two with renin inhibitors, is contraindicated, since they lead

to an increase in adverse effects without decreasing CV outcomes.⁵⁶⁸⁻⁵⁶⁹

Chart 9.3 lists the major clinical trials that used combinations of antihypertensive medications, while Chart 9.4 shows the primary levels of evidence and level of recommendation of pharmacological treatments. Figure 9.1 shows the usual steps of combining medications for HT control.

Key Takeaways

The primary objectives of antihypertensive treatment are lowering blood pressure and the risk of CV outcomes and mortality associated with hypertension.

Pharmacological treatment should be combined with nonpharmacological measures, and the preferred antihypertensive classes for use in monotherapy or combination therapies are: thiazide or thiazide-like diuretics, CCBs, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and beta-blockers (with specific indications).

Combining medications is the first recommended strategy for moderate- to high-risk stage 1 hypertensive patients and stages 2 and 3 patients, preferably in a single pill. Monotherapy should be considered for low-risk stage 1 hypertensive patients and for oldest old and/or frail individuals.

Two-drug treatments should begin with an ACEI or ARB combined with a thiazide or thiazide-like DIU or a CCB. In nonobese high-risk patients, CCB combinations are preferred.

When two medications combined are unable to control BP, patients should be prescribed three drugs, usually an ACEI or ARB combined with a thiazide or thiazide-like DIU and a CCB; if needed, add spironolactone next.

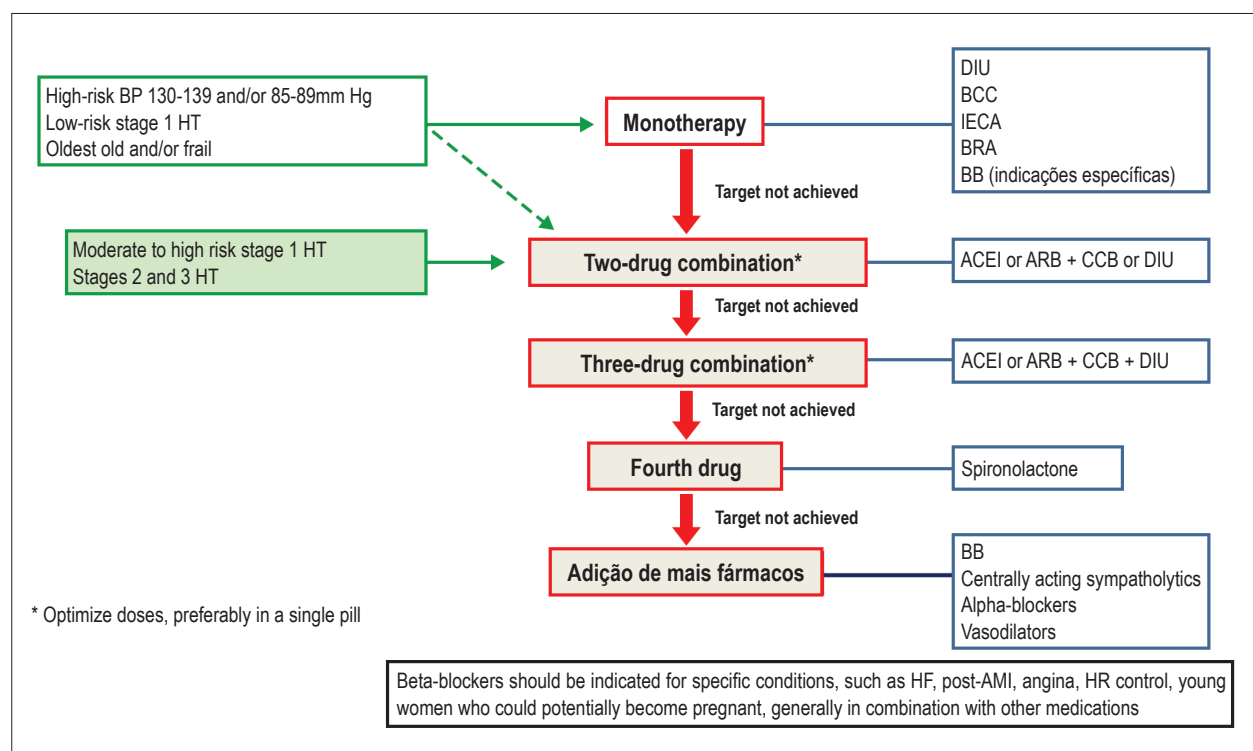


Figure 9.1 – Flow chart for pharmacological treatment.

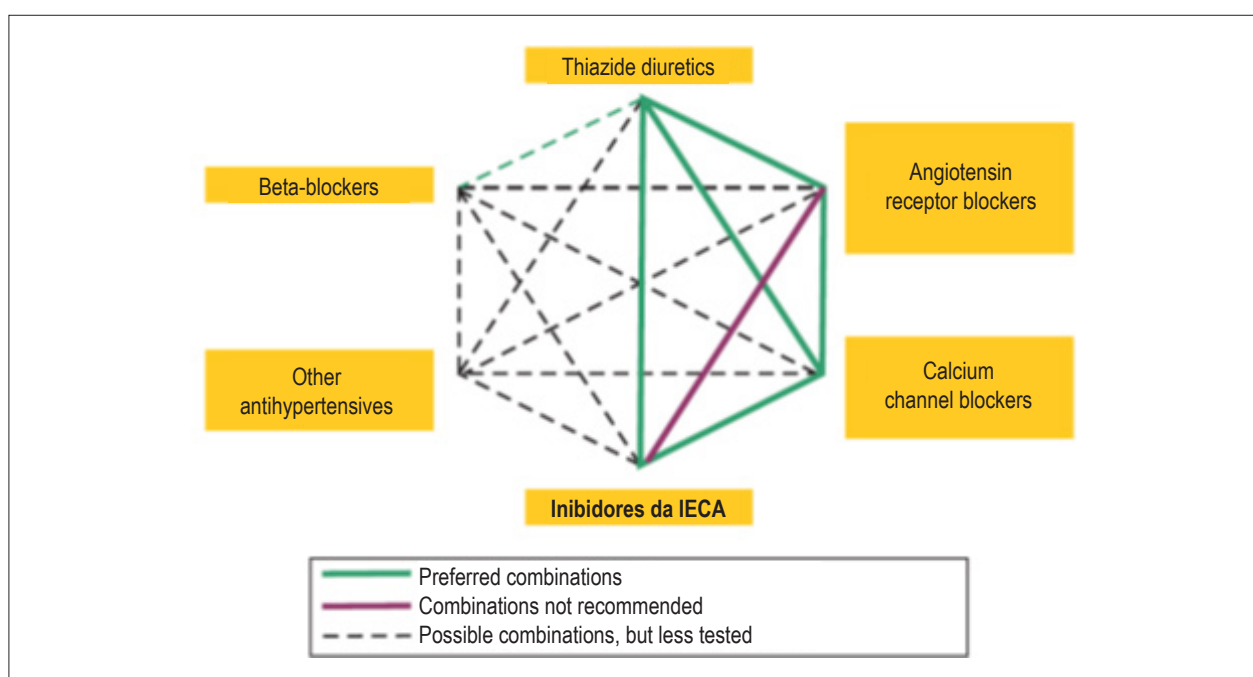


Figure 9.2 – Preferential associations of drugs according to mechanisms of action and synergy.
Source: Malachias et al., 2016.164

Chart 9.1 – Onset of treatment with lifestyle interventions and pharmacological treatment according to blood pressure, age, and cardiovascular risk

Status	Scope	Recommendation	Class	Level of evidence
Onset of lifestyle interventions	All stages of hypertension and blood pressure 130-139/85-89mm Hg	To diagnosis	I	A
Onset of pharmacological treatment	Stage 2 and 3 hypertensive patients	To diagnosis	I	A
	Stage 1 hypertensives at moderate to high cardiovascular risk	To diagnosis	I	B
	Stage 1 hypertensives and low cardiovascular risk Individuals with BP 130-139/85-89 mm Hg and preexisting CVD or at high cardiovascular risk	Wait 3 months for effects of lifestyle interventions	IIa	B
	Frail older adults and/or oldest old hypertensives	SBP $\geq$ 160 mm Hg	I	B
	Healthy older hypertensive patients	SBP $\geq$ 140mm Hg	I	A
	Individuals with BP 130-139/85-89 mm Hg without preexisting CVD and at low to moderate cardiovascular risk	Not recommended	III	

Guidelines

Chart 9.2 – List of antihypertensive medications available in Brazil

Class	Class and Medication	Usual daily dose (mg)	Freq.*	Comments and recommendations
Thiazide and thiazide-like diuretics	Hydrochlorothiazide	25-50	1	Higher doses of thiazides and thiazide-like medications increase the diuretic effect without increasing antihypertensive action.
	Chlorthalidone	12.5-25	1	
	Indapamide	1.5	1	
Loop diuretics	Furosemide	20-240	1-3	Used in chronic renal failure (CRF), congestive heart failure (CHF), and fluid retention conditions (edema).
	Bumetanide	1-4	1-3	
Potassium-sparing diuretics	Spironolactone	25-100	1-2	May cause hyperkalemia, particularly in CRF and when associated with ARBs or ACE inhibitors.
	Amiloride	2.5-5	1	Available only in combination with hydrochlorothiazide or chlorthalidone
Dihydropyridine calcium channel blockers (CCBs)	Amlodipine	2.5-10	1	Avoid use in patients with heart failure and reduced ejection fraction. May cause lower limb edema depending on dose.
	Felodipine	2.5-10	1	
	Nifedipine	10-60	1-3	
	Nitrendipine	10-30	1	
	Manidipine	10-30	1	
	Lacidipine	2-6	1	
	Lercanidipine	10-20	1	
	Levamlodipine	2.5-5	1	
Nondihydropyridine calcium channel blockers (CCBs)	Verapamil	120-360	1-2	Avoid use in patients with heart failure and reduced ejection fraction. Avoid association with beta-blockers and in patients with bradycardia.
	Diltiazem	80-240	1-2	
Angiotensin-converting enzyme inhibitors (ACEIs)	Captopril	25-150	2-3	Avoid use in women of childbearing age due to the high risk of fetal malformations and other gestational complications. Contraindicated in combination with other renin-angiotensin-aldosterone system inhibitors, except spironolactone for CHF. Risk of hyperkalemia for patients suffering from renal failure or receiving potassium supplementation.
	Enalapril	5-40	1-2	
	Benazepril	10-40	1-2	
	Lisinopril	10-40	1	
	Fosinopril	10-40	1	
	Ramipril	2.5-20	1-2	
	Perindopril	2.5-10	1	
Angiotensin II AT ₁ receptor blockers (ARBs)	Losartan	50-100	1-2	Same recommendations as ACEIs.
	Valsartan	80-320	1	
	Irbesartan	150-300	1	
	Candesartan	8-32	1	
	Olmesartan	20-40	1	
	Telmisartan	20-80	1	
Noncardioselective beta-blockers (BBs)	Propranolol	80-320	2-3	Avoid sudden withdraw of BBs, as it may cause reflex tachycardia and discomfort.
	Nadolol	40-160	1	
	Pindolol	10-60	1	
Cardioselective beta-blockers	Atenolol	50-100	1-2	Vasodilatory action via nitric oxide.
	Metoprolol	50-200	1	
	Bisoprolol	5-20	1	
	Nebivolol	2.5-10	1	
	Carvedilol	12.5-50	1-2	Alpha-blocker effect produces less bradycardia.

Centrally acting sympatholytics	Methyldopa	500-2.000	2	Abrupt clonidine withdraw may cause rebound hypertension (hypertensive crisis) via catecholamine release at synaptic endings.
	Clonidine	0.2-0.9	2	
	Rilmenidine	1-2	1-2	
Alpha-blockers	Prazosine	1-20	2-3	Initiate with low dose before lying down since it may trigger orthostatic hypotension. Progressively increase every 2 days. Other alpha-blockers are exclusively available for benign prostate hyperplasia (tamsulosin, alfuzosin, silodosin).
	Doxazosin	1-16	1	
Direct-acting vasodilators	Hydralazine	50-200	2-3	May cause sodium and fluid retention, hypervolemia, and reflex tachycardia. Must be used in combination with loop diuretic. Lupus-like syndrome at high dose.
Direct renin inhibitors	Aliskiren	150-300	1	Same recommendations as ACEIs and ARBs.

Chart 9.3 – Drug combination studies for hypertension treatment

Study	Comparator regimen	Patient profile	Difference in SBP (mm Hg)	Primary outcome (% relative risk reduction)	p
Combinations of diuretics					
PREVER ¹⁷⁹ (amiloride + chlorthalidone)	Losartan	Stage 1 hypertensive patients	-2.2	Not assessed. Greater SBP decrease with diuretics without glucose increase	–
Association of ACE inhibitors and diuretics					
PROGRESS ²⁹¹ (perindopril + indapamide)	Placebo	Prior stroke or TIA	-9	-28% stroke	< 0.001
ADVANCE ⁵⁵⁹ (perindopril + indapamide)	Placebo	Diabetes	-5.6	-9% macrovascular and microvascular events	0.04
HYVET ⁵⁶⁰ (indapamide + perindopril)	Placebo	Hypertensive patients ≥ 80 years	-15	-34% CV events	< 0.001
Combination of ACE inhibitors and calcium channel blockers (amlodipine)					
ACCOMPLISH ⁵⁵⁴ (benazepril + amlodipine)	Benazepril + diuretic	High-risk hypertensive patients	-0.9	-19.6% compound CV events	< 0.001
ASCOT BPLA ⁵⁵⁸ (amlodipine + perindopril)	Beta-blocker + diuretic	Hypertensive patients with 3 or more risk factors	-2.7	Difference not significant *	NS
Combination of angiotensin receptor blockers (olmesartan) and calcium channel blockers					
COLM ⁵⁷⁰ (olmesartan + CCB)	Olmesartan + diuretic	Older hypertensive Japanese patients with CV disease or risk factors	0	Difference not significant	NS
Combination of angiotensin receptor blockers and diuretics					
LIFE ⁵²⁶ (losartan + diuretic)	Beta-blocker + diuretic	Hypertensive patients with LVH	-1.1	-13% CV events	0.02
Combination of calcium channel blockers and diuretics					
FEVER ⁵⁷¹ (felodipine + diuretic)	Diuretic + placebo	Hypertensive patients	-4	-34% CV events	< 0.001
Combination of calcium channel blockers and ACE inhibitors					
SYST-EUR ⁵⁷² (ACEI + ARB + diuretic)	Placebo	Older adults with ISH	-10	-31% CV events	< 0.001
SYST-CHINA ⁵⁷³ (ACEI + ARB + diuretic)	Placebo	Older adults with ISH	-9	-37% CV events	< 0.004
Combinations of beta-blockers and diuretics					
Coope and Warrender ⁵⁷⁴ (atenolol and diuretic)	Placebo	Older hypertensive patients	-18	-42% stroke	< 0.003

Guidelines

SHEP ⁵⁰⁹ (chlorthalidone and atenolol)	Placebo	Older hypertensive patients	-13	-36% stroke	< 0.001
STOP-H ⁵⁶¹ (beta-blocker and diuretic)	Placebo	Older adults with ISH	-23	-40% CV events	< 0.004
STOP-H2 ⁵⁶² (ACEI and CCB)	Standard treatment (BB and diuretic)	Older hypertensive patients	0	No difference in CV events	–
Combination of two renin-angiotensin system antagonists					
ONTARGET ⁵⁶⁸ (telmisartan + ramipril)	ACEI or ARB	High-risk patients	–	Worse renal outcomes	–
ALTITUDE ⁵⁶⁹ (aliskiren + ARB)	ACEI or ARB	High-risk diabetic patients	–	Worse renal outcomes	–
Combination of fixed-dose calcium channel blocker, angiotensin receptor blocker, and diuretic					
Calhoun et al. ⁵⁶³ (ARB + diuretic + CCB)	ARB + diuretic ^a or CCB ^b + diuretic or ARB + C ^c Bc	Stage 2 and 3 hypertensive patients	a: -7.6 b: -8.2 c: -6.2	Not assessed	–
TRIUMPH ⁵⁷⁵ (telmisartan + amlodipine + chlorthalidone)	Usual treatment at the end of 6 months: Monotherapy in 65% and two-drug combination in 29%	Hypertensive patients	-8.8	Not assessed	–

Adapted from ESC, 2018.³⁷ ISH: isolated systolic hypertension; LVH: left ventricular hypertrophy; NS: not significant; TIA: transient ischemic attack. * significant differences in various secondary outcomes favoring ACEI + amlodipine; (a) ARB + diuretic (b) ARB + diuretic or CCB (c) diuretic or ARB + CCB.

Chart 9.4 – Pharmacological treatment: levels of evidence and level of recommendation

Drug combinations	LE	LR
The preferential medication classes for antihypertensive treatment are thiazide or thiazide-like DIUs, CCBs, ACEIs, and ARBs, as they have been shown to effectively lower BP and the risk of CV outcomes. BBs should be considered for specific clinical scenarios (CAD, HF and HR control)	A	I
HT treatment may be initiated with two-drug class combinations starting in stage 1 HT	B	I
Two-drug treatments should begin with an ACEI or ARB combined with a thiazide or thiazide-like DIU or a CCB	A	I
HT treatment for high CV risk patients combining an ACEI and a dihydropyridine CCB is preferred over combining an ACEI and a thiazide DIU for nonobese patients	B	I
When two medications combined are unable to control BP, patients should be prescribed three drugs, usually an ACEI or ARB combined with a thiazide or thiazide-like DIU and a CCB	A	I
When three medications combined are unable to control BP, preference should be given to adding spironolactone to the therapy regimen	B	I
HT treatment with fixed combinations enables higher adherence rates	B	IIa
HT treatment combining two renin-angiotensin system antagonists is contraindicated	A	III

10. Hypertension And Associated Clinical Conditions

10.1. Diabetes Mellitus (DM)

Hypertension (HT) is a frequent finding in DM patients, especially type 2 diabetes. Evidence shows the benefits of lowering BP for this population, with subsequent lower rates of macro and microvascular events and lower mortality. These include lower rates of chronic kidney disease (CKD),^{307,329} diabetic retinopathy, and albuminuria.⁵⁷⁶ Current data show a major reduction in cardiovascular (CV) risk for DM patients, though it remains a high-prevalence illness and an important risk factor (RF) for cardiovascular disease (CVD).^{577,578} The relationship between DM and HT provides relevant data, such as the presence of HT in 40% of recently-diagnosed patients with type 2 DM⁵⁷⁹ and that 50% of type DM patients become hypertensive before the onset of albuminuria. This population is at high CV risk, so assessing urinary albumin and creatinine excretion, fundus health, and dysautonomia should be part of the investigation.⁵⁸⁰

10.1.1. Treatment Objectives

Randomized clinical trials show the benefits of antihypertensive treatment for this population, such as the lower incidence of stroke, coronary syndromes, and CKD when BP levels below 140/90 mm Hg are achieved. In a meta-analysis of 13 clinical trials involving DM patients, systolic blood pressure (PAS) between 131 and 135 mm Hg decreased all-cause mortality risk by 13%, while more intensive SBP control to ≤ 130 mm Hg was associated with a greater decrease in strokes.⁵⁸¹ A second meta-analysis found significant decreases in mortality from achieving a mean SBP of 138 mm Hg and a significant decrease in strokes with a mean of 122 mm Hg.⁵⁷⁶ Therefore, BP control is important to lower the risk of micro and macrovascular complications and should be maintained if these benefits are to be sustained (LR: I, LE: A).

Rigorous nonpharmacological treatment is required for all diabetic hypertensive patients. Office BP $\geq 140/90$ mm Hg indicates the need for pharmacological treatment. All medications used in lowering BP may be administered to diabetic patients. The evidence supports the preferential use of RAAS blockers, particularly for patients with end-organ damage (EOD).^{526,582-584} BP often requires combination therapy, and calcium channel blockers (CCBs) and/or diuretics (DIUs) are the recommended drug classes for combinations with RAAS inhibitors.^{506,585} Combining two or more classes in a single galenic formulation should be considered, taking into account that adherence to treatment is paramount in this high-risk population.

10.2. Metabolic Syndrome (MS)

MS is characterized by a set of CV risk factors, including central obesity, high glycemia, and typical dyslipidemia (high triglycerides and low HDL-cholesterol levels) associated with increased BP.⁵⁸⁶⁻⁵⁸⁸ These metabolic changes are found in 30 to 40% of HT patients,⁵⁸⁹ and the presence of high blood

pressure (BP) in MS increases global CV risk by triggering mechanisms associated with prothrombotic and pro-inflammatory states.⁵⁹⁰ Therefore, investigating metabolic alterations from MS and central obesity is indispensable for HT patients. Lifestyle changes (LSCs) for weight loss, lower sodium intake, and controlling dysglycemia and dyslipidemia are recommended for all patients in these conditions.⁵⁹¹ Pharmacological treatment should be initiated whenever BP $\geq 140/90$ mm Hg, since there is no evidence of benefit in the use of antihypertensive agents for MS with normal BP levels.⁵⁹² The choice of antihypertensive medications should prioritize therapeutic classes capable of improving insulin resistance, or at least not make it worse, such as angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II AT₁ receptor blockers (ARBs), and CCBs. DIUs and beta-blockers (BBs), except for direct-acting vasodilators, may be indicated as additional medications.⁵⁹³

10.3. Coronary Artery Disease (CAD)

Robust epidemiological evidence connects HT to CAD. Data from the INTERHEART study show that 25% of infarctions (AMI) may be attributable to HT.²⁸⁶ A meta-analysis assessing the impact of BP found a mean decrease of 17% in CAD for every 10 mm Hg decrease in SBP.⁸⁵

Treatment for HT associated with CAD, which includes post-AMI patients with chest angina and myocardial revascularization (MRV), should preferably comprise BBs, ACEIs, or ARBs, in addition to statins and acetylsalicylic acid. Beta-blockers are beneficial after AMI, especially within 2 years from the acute event.⁸⁶ Similarly, ACEIs and ARBs tested on that condition have also proven beneficial.^{83,594,595} In patients with chronic CAD and multiple risk factors, such as HT, ACEIs have been found to lower relevant clinical outcomes⁸⁶ (LE: I; LR: A).

Regarding BP target, it is worth considering the likelihood of the J-curve effect, found in different studies,⁵⁹⁷⁻⁶⁰⁰ in which the excessive BP decreases, mainly in diastolic blood pressure (DBP), can trigger CV events in patients with obstructive CAD. Thus, the goal is to achieve SBP < 130 mm Hg and DBP < 80 mm Hg (LR: IIa; LE: B), while levels below 120/70 mm Hg should be avoided.⁶⁰¹ Additional medications, such as CCBs and thiazide diuretics,⁸⁶ may be administered to achieve those BP targets.

10.4. Hypertension in Chronic Kidney Disease (CKD)

10.4.1. Patient in Conservative Treatment: Goals and Treatment

In CKD, BP levels to be achieved remain undetermined, and the evidence depends on associated morbidities.⁶⁰² Nondiabetic patients treated with strict targets ($< 130/80$ mm Hg) showed slower disease progression only in subgroups with proteinuria, and CV events could not be assessed^{603,604} (LR: IIa; LE: A). On the other hand, a meta-analysis has found lower mortality with intensive treatment for HT.⁶⁰⁵ In diabetic patients, strict targets led to decreased albuminuria, improved retinopathy and fewer strokes, but no impact on other CV outcomes^{581,606,607} (LR: IIa; LE: A).

Guidelines

A study with 9361 nondiabetic patients, out of which 2646 had CKD, found a decrease in CV events in the order of 25% for the treatment group that sought SBP below 120 mm Hg. This suggests the probable benefits provided by this strategy in CV protection for CKD patients⁸⁶ (LR: I; LE: A).

In terms of pharmacological treatment, ACEIs or ARBs are indicated for hypertensive patients with or without albuminuria, and its use in combination therapy is proscribed⁶⁰⁸ (LR: I; LE: A). Thiazide⁸³ or loop diuretics, the latter for G4 and G5 CKD, and CCBs are effective, especially in combination with ACEIs or ARBs⁶⁰⁹ (LR: I; LE: A). BBs are indicated for CAD and associated heart failure (HF).⁶¹⁰ Mineralocorticoid receptor antagonists lower proteinuria, but may cause hyperkalemia. Clinical trials of new antagonists in this class are in progress.⁶¹¹

This guideline recommends a BP target < 130/80 mm Hg for adults with HT and CKD, whether diabetic or not. Stricter targets may be sought in select cases, under strict vigilance and after patients have been informed of the risks.

10.4.2. Patients in Renal Replacement Therapy (RRT): Goals and Treatment

Managing HT in patients undergoing dialysis treatment can be a challenge, especially due to the volume overload that increases BP variability, overestimating it pre-dialysis and overestimating it afterward.⁶¹² There is no evidence regarding optimum BP levels for dialysis patients, but the most often accepted values immediately before and after hemodialysis (HD) are $\leq 140/90$ mm Hg and $\leq 130/80$ mm Hg, respectively^{613,614} (LR: IIa; LE: C). For these patients, there is a (paradoxical) U-shaped association between SBP measured at the dialysis unit and CVD risk, with values above 160 mm Hg or < 110 mm Hg implicated in increased mortality^{614,615} (LR: IIa; LE: B).

In this population, home BP readings are more reproducible, provide relevant information for therapeutic decisions, and are better associated with BP control⁶¹³ (LR: IIa; LE: B). Systolic means from home measurements are linearly associated with increased CV risk.^{615,616} In addition to hypervolemia, arterial stiffness is an important cause of systolic hypertension in stage 5D CKD patients. This specific phenotype reflects the acceleration of the atherosclerosis process and premature vascular aging in this population.⁶¹⁶ Other mechanisms, such as sleep apnea,⁶¹⁷ sympathetic hyperactivity,⁶¹⁸ and erythropoietin use, should also be considered.⁶¹⁶

HT treatment for patients undergoing dialysis treatment is only effective for 1/3 of individuals, and is even harder to achieve due to hemodynamic instability during sessions, which may cause intradialytic hypotension or hypertension, leading to poorer CV prognoses⁶¹⁹ (LR: IIa; LE: B).

Treatment should start with measures focusing on achieving “dry weight,” such as salt and water restriction and ultrafiltration in dialysis⁶²⁰ (LR: IIa; LE: A). Regardless, approximately 60% of dialysis patients require three or more antihypertensives, in several combinations, to control HT⁶²⁰ (LR: IIa; LE: A). In this population, sympathetic nervous system (SNS) hyperactivity has a major role in the origins of HT and in CVD. Accordingly, beta blockade was superior to ACE

inhibition in preventing CV morbidity and in BP control for patients with left ventricular hypertrophy (LVH) undergoing hemodialysis treatment.⁶¹⁸ In kidney transplant patients, CCBs and ARBs are the first option, since there is evidence that they prevent graft loss^{621,622} (LR: I; LE: A).

This guideline suggests the individualization of treatment in RRT, considering comorbidities, pharmacokinetics, and the cardioprotective effect of medications.

10.5. Heart Failure (HF)

HT has a key role in the pathophysiology of HF, leading to the onset of LVH and left ventricular diastolic and systolic dysfunction.⁶²³⁻⁶²⁵ It is the greatest RF for the disease, and usually precedes the clinical syndrome by several years. In HF with preserved ejection fraction (HFpEF), HT is even more frequent, and it is the most common RF, with prevalence rates of up to 90%.⁶²⁶

Early diagnosis of HT and adequate treatment can significantly lower the risk of developing HF, especially for older adults. Pharmacological strategies for BP control promote decreases of approximately 50% in HF incidence in adults, and a 64% decrease for those age 80 and older.^{560,627-628} The SPRINT trial, with a stronger SBP decrease target (< 120 mm Hg) for a high CV risk population, found a decrease of 27% in total mortality and 38% in progression to HF.^{86,629} The impact of antihypertensive treatment on preventing HF has been found for various classes of antihypertensive medication, such as BBs, DIUs, CCBs, and ACEIs.⁶³⁰

BP targets in HF settings should be similar to those recommended for high CV risk individuals, ie, < 130/80 mm Hg.⁶³¹ HT treatment in HF should consider its presentation, ie, whether with preserved ejection fraction (HFpEF) or reduced ejection fraction (HFrEF) (Chart 10.1). The first therapeutic antihypertensive option for HFrEF should supplement medications promoting neurohormonal blockade, be dose-optimized, and have scientific evidence proving it reduces mortality.⁶³² These medications are RAAS blockers, BBs, and aldosterone antagonists. The sacubitril/valsartane combination is a new treatment option impacting mortality reduction in HFrEF, but still with no evidence of benefits for HT.⁶³³

If blood pressure levels remain high despite the neurohormonal blockade, they can also be combined with DIUs; vasodilator hydralazine-nitrate combination; or dihydropyridine CCBs. Nondihydropyridine CCBs, such as diltiazem and verapamil, and BBs are contraindicated.⁶³¹

Due to the strong association between HFpEF and HT, antihypertensive treatment is indicated for most patients. Diuretics should be used for BP control and for symptoms connected to hypervolemia, but randomized clinical trials have not found lower mortality rates for HFpEF patients. Despite the lack of evidence about the benefits of SNS and RAAS blockers to lower HFpEF mortality, these substances should still be used for blood pressure control.⁶³⁴⁻⁶³⁹ Other classes of antihypertensives may also be used.

The relationship between SBP levels and CV mortality follows a J-shaped curve, especially for HFrEF.^{640,641} Data from clinical trials such as Copernicus, DigTrial, Val-HeFT and

PARADIGM-HF^{318,642-644} have verified the relationship between lower BP values and higher mortality rates.

In HFpEF, the association between BP levels and clinical outcomes remains controversial.^{317,318} In that patient group, BP levels should be kept within the 120-129/70-79 mm Hg target range.

10.6. Hemorrhagic Stroke and Ischemic Stroke

Ischemic and hemorrhagic stroke are the most frequent manifestations of the vascular damage caused by HT and are the leading cause of death and impairment for those patients.²⁹² Preventing all forms of stroke is possible by achieving BP target levels with adequate treatment (see Chapter 6)^{291,645-652} (LR: IIa; LE: B).

10.6.1. Hemorrhagic Stroke

High BP increases the likelihood of hematoma expansion,

leading to worse prognosis and increased risk of death.⁶⁵³ Robust studies suggest that lowering BP (within 6 h) to values <140/90 mm Hg does not lower the rates of primary events, including mortality.⁶⁵⁴ Therefore, immediately lowering BP for hemorrhagic stroke cases is not recommended unless SBP levels are > 220 mm Hg.

10.6.2. Ischemic Stroke

The benefits of lowering BP for strokes are less clear, but should be considered for thrombolysis candidates, since, in their case, if BP > 180/105 mm Hg, there may be a greater risk of hemorrhaging.^{655,656} A meta-analysis suggests that lowering blood pressure in ischemic strokes may have a neutral effect on mortality.^{657,658}

Chart 10.2, adapted from the ESC and ESH guidelines,³⁷ lists therapeutic targets and recommendations for acute stroke and cerebrovascular disease patients.

Key Takeaways

BP control is important to lower the risk of micro and macrovascular complications and should be maintained if these benefits are to be sustained (LR: I, LE: A). Office BP $\geq 140/90$ mm Hg indicates the need for pharmacological treatment preferably accompanied by LSCs and the use of RAAS blockers, while DIUs and CCBs may be added to achieve a blood-pressure target of <140/90 mm Hg.

Pharmacological treatment should be initiated for MS whenever BP $\geq 140/90$ mm Hg, prioritizing the use of metabolically neutral antihypertensives or those that improve insulin sensitivity, such as ACEIs, ARBs, and CCBs.

In CKD patients, the BP target is <130/80 mm Hg, and may be stricter in select cases. In dialysis patients, achieving "dry weight" is key. Approximately 60% of dialysis patients require 3 or more antihypertensives, in several combinations, to control HT. For kidney transplant patients, CCBs and ARBs represent their first therapeutic option.

Immediately lowering BP for hemorrhagic stroke cases is not recommended unless SBP levels are ≥ 220 mm Hg; if so, use IV medications, with target SBP 180 mm Hg.

For HT and HF (PEF and REF) patients, the blood-pressure target should be <130/80 mm Hg. In HFrEF, blood pressure levels should be controlled with BBs, ARBs, and spironolactone, while all antihypertensives may be used for HFpEF.

Treatment for HT associated with CAD, which includes post-AMI patients with chest angina and myocardial revascularization (MRV), should preferably comprise beta-blockers, ACEIs, or ARBs, in addition to statins and acetylsalicylic acid, with a blood-pressure target of < 130/80 mm Hg.

J- or U-shaped curves are often seen in CAD patients, and levels below 120/70 mm Hg are to be avoided. In CKD, especially in dialysis patients, SBP levels above 160 mm Hg or <110 mm Hg have been implicated in increased mortality.

Chart 10.1 – Antihypertensive treatment for heart failure patients

Antihypertensive treatment for HF patients

Recommendations	RC	LE
The blood-pressure target for HT and HF patients (REF and PEF) should be < 130/80 mm Hg	I	C
In HFrEF, antihypertensive medications with proven effect on mortality rates (BBs/ACEIs/ARBs/spironolactone) should be used	I	A
In HFpEF, all antihypertensive drugs may be used.	I	C
Nondihydropyridine calcium channel blockers and alpha-blockers are contraindicated for HFrEF.	III	C

HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LE: level of evidence; RC: recommendation class.

Chart 10.2 – Therapeutic targets and recommendations for acute stroke and cerebrovascular disease patients

Recommendations	RC	LE
AVEH Do not lower BP in patients with SBP < 220 mm Hg If SBP ≥ 220 mm Hg, use IV medications, with target SBP 180 mm Hg	III IIa	A B
AVEI Lowering BP is not recommended, except for patients eligible for thrombolysis. In that case, maintain BP < 180/105 mm Hg	III IIa	B B
Transient ischemic attack Immediate decrease	I	A
Goal: keep SBP between 120 and 130 mm Hg after event	I	A
Secondary prevention Use renin-angiotensin system blockers + calcium channel blockers or thiazide diuretics	I	A

LE: level of evidence; RC: recommendation class; SBP: systolic blood pressure.

11. Hypertension in Pregnancy

11.1 Epidemiology

Hypertensive disorders of pregnancy is one of the leading causes of maternal and perinatal mortality throughout the world. From 0.9 to 1.5% of pregnant women have chronic hypertension, and it is estimated that pre-eclampsia (PE) complicates 2 to 8% of pregnancies globally.^{659,660} Those syndromes are causal factors associated with perinatal and maternal death, may permanently impair maternal health and may cause major issues from preterm birth associated with early indications for intervention (elective preterm birth).⁶⁶⁰ In Brazil, PE is the leading cause of provider-initiated preterm birth,⁶⁶¹ and the estimated incidence rates are 1.5% for PE and 0.6% for eclampsia.⁶⁶² The prevalence of eclampsia in the more developed regions of Brazil is 0.2%, with an 0.8% mortality rate,⁶⁶¹ while prevalence rates in less developed regions rise to 8.1%, with a corresponding mortality rate of 22.0%.⁶⁶³

11.2. Classification of Hypertension in Pregnancy

We recommend the definitions and classification put forth by the *American College of Obstetricians and Gynecologists* (ACOG),^{664,665} which can be found in Chart 11.1 (LR: IIb, LE: B).

11.3. Concept and Diagnostic Criteria

Hypertension in pregnancy is defined as the presence of systolic blood pressure (SBP) ≥ 140 mm Hg and/or diastolic blood pressure (DBP) ≥ 90 mm Hg, considering the fifth Korotkoff sound, confirmed by another measurement after a 4-hour interval. Ideally, the measurement should be taken with the patient sitting down or in left lateral decubitus position, with a properly sized cuff. The manual auscultatory method is the gold standard, since automated devices may underestimate blood pressure (BP), especially in severe pre-eclampsia. Ambulatory blood pressure monitoring (ABPM) is superior to BP measurements at the physician's office and home blood pressure monitoring (HBPM) for nonpregnant women. For pregnant women, it helps avoid unnecessary treatment for white coat hypertension (WCH) and is useful in managing high-risk gestational hypertension and in detecting

masked hypertension.³⁷ The role of ABPM and HBPM is still controversial in pregnancy. The International Society for the Study of Hypertension in Pregnancy (ISSHP) recommends the use of ABPM before the 20th gestational week and HBPM for follow-up.⁶⁶⁶ The cutoff point for HT is ≥ 135/85 mm Hg for daytime ABPM and ≥ 130/80 mm Hg for HBPM (Chapter 3).

The definition and classification of hypertensive disorders in pregnancy can be found in Chart 11.1.

11.4. Prediction and prevention of pre-eclampsia

Calcium supplementation (> 1 g/day) is not recommended for pregnant women with normal calcium intake⁶⁶⁷ (LR: III, LE: A), but is recommended for those with low calcium intake and at intermediate to high risk of pre-eclampsia⁶⁶⁷ (LR: I, LE: A).

Low doses of acetylsalicylic acid (ASA) (75- 150 mg/day) at the end of the first gestational trimester can be useful for primary prevention of pre-eclampsia in pregnant women at intermediate to high risk of pre-eclampsia⁶⁶⁸⁻⁶⁷⁰ (LR: I, LE: A). However, its use is not recommended in the absence of risk⁶⁶⁹ (LR: III, LE: A).

Pre-eclampsia prediction should preferentially be performed during the 1st semester using assessment methods that take into consideration maternal clinical history (risk factors) associated with Doppler ultrasound to check for flow resistance in the uterine arteries. There are also promising laboratory tests to assess angiogenesis, such as serum soluble endoglin, PlGF (placental endothelial growth factor), sFlt-1 (soluble fms-like tyrosine kinase receptor-1), and sFlt-1/PlGF ratio, but which are still not available in clinical practice.⁶⁶⁶

In patients at high risk for PE, the use of calcium for low-intake populations (< 600 mg/day), a dose of 1.0 to 2g/day effectively lowers the risk of PE.⁶⁶⁷ Chart 11.2 summarizes the use of ASA at low doses (75-150 mg/day) for eclampsia prevention. It should be initiated preferably before the 16th week, with no increase in maternal or fetal complications, and is recommended by international guidelines such as NICE 2019,⁶⁷¹ the WHO's⁶⁷² and that of the American College of Obstetricians and Gynecologists (ACOG).⁶⁶⁴ A study⁶⁷⁰ involving 1776 patients, comparing acetylsalicylic acid at 150 mg and a placebo, starting at 11 to 14 weeks, found a total

event rate (PE) of 1.6% for the acetylsalicylic acid group and 4.3% for the placebo group (OR: 0.38, 95% CI 0.2 to 0.74, $p = 0.004$). This confirms the protective effect of acetylsalicylic acid for high-risk pregnant women.

In its 2019 report on screening and prevention,⁶⁷³ the International Federation of Gynecology and Obstetrics (FIGO) suggests the use of the Fetal Medicine Foundation risk calculator to determine when acetylsalicylic acid is indicated in pre-eclampsia prevention. This useful tool is available at <https://fetalmedicine.org/research/assess/pre-eclampsia/first-trimester>.

11.5. Nonpharmacological Treatment

For SBP persisting above 160 mm Hg for more than 15 minutes, nonpharmacological treatment alone should not be used (LR: III, LE: B). Relative rest at hospital or day hospital with monitoring is suggested for pre-eclampsia (LR: IIa, LE: B). Hospitalization is indicated for patients with severe gestational hypertension (LR: I, LE: B).

Nonpharmacological treatment alone should not be used to treat severe HT persisting for ≥ 15 min⁶⁷⁴ to prevent irreversible neurological damage, since SBP values > 155 mm Hg, especially > 160 mm Hg, are detected immediately before a stroke.⁶⁷⁵ Severe diastolic hypertension (> 105 or 110 mm Hg) does not develop before most strokes in pregnant women with severe pre-eclampsia.⁶⁷⁶

A systematic review found no differences in outcomes between strict rest and relative rest for pregnant women with hypertension and proteinuria.⁶⁷⁷ Relative rest at hospital, as compared with routine house activity, reduces the risk of severe hypertension. Rest is not routinely indicated for gestational hypertension.⁶⁷⁷ Prenatal care units and hospital admissions have similar clinical outcomes for mothers and newborns, but women may prefer treatment at day hospitals.⁶⁷⁸

Although there is no indication for specific care during hospitalization, maternal and fetal monitoring is required. Blood pressure should be measured periodically, with daily weight and diuresis assessment, and patients should be instructed about warning signs. Laboratory tests (CBC with platelet count, liver enzymes, uric acid, creatinine and proteinuria) should be performed once to twice a week. Fetal follow-up comprises assessment of growth, movements, well-being and biophysical profile, as well as ultrasound.

11.6. Expectant Management

Expectant management is not recommended after 37 gestational weeks for women with gestational hypertension and prehypertension⁶⁷⁹ (LR: III, LE: B). Expectant management is suggested between the 34th and 37th gestational weeks for stable women, without clinical worsening or severe hypertension⁶⁸⁰ (LR: IIa, LE: B).

Premature delivery for patients with PE can be associated with decreased mortality.⁶⁸¹ Optimum delivery time before the 32nd to 34th weeks poses a dilemma due to the uncertainty in the balance between maternal safety (end of pregnancy) and fetal maturity (expectant).⁶⁸¹ After the 34th week, survival is high and baby and placenta delivery is effective in developed

countries.⁶⁸¹ Physicians tend to delay birth until the 37th week, if it is considered safe.

The HYPITAT study compared induction of labor versus expectant monitoring for severe hypertension or PE without signs of severity (at the time, called mild PE) after the 36th week.⁶⁷⁹ Women in the intervention group had a 29% lower risk of worse maternal outcomes, without affecting neonatal outcomes, suggesting that expectant treatment up to 37 weeks is not indicated.⁶⁷⁹ In the HYPITAT-II study, in nonsevere HT between the 34th and 37th gestational weeks, expectant management increased maternal risk as compared to immediate delivery, but decreased the occurrence of neonatal respiratory distress syndrome.⁶⁸⁰ Therefore, immediate delivery is not justified, and expectant monitoring should be considered until the clinical situation worsens. If labor inducing labor before the 34th week is indicated and both maternal and fetal clinical statuses allow a 48-hour wait to see if the situation resolves, corticosteroid use for fetal pulmonary maturation may be considered.⁶⁸²

11.7. Pharmacological Treatment

Urgent pharmacological treatment is indicated for severe hypertension^{674,675} and in the presence of warning signs (LR: I, LE: B). There is no consensus BP value to indicate when pharmacological treatment should be initiated. Pharmacological treatment should be initiated when BP is above 150-160/100-110 mm Hg^{665,674,676} with the goal of keeping it in the 120-160/80-100 mm Hg range (LR: IIb, LE: B).

The choice of the antihypertensive medication depends on the attending physician's experience and familiarity with the drug chosen and its side effects⁶⁸³ (LR: IIb, LE: B). The use of ACEIs, ARBs, and direct renin inhibitors is contraindicated in pregnancy (LR: I, LE: B), and atenolol and prazosin should be avoided if possible^{683,684} (LR: IIa, LE: B).

Magnesium sulfate is recommended for eclampsia prevention and treatment (LR: I, LE: B). To avoid maternal deaths, SBP > 150 -160 mm Hg should indicate urgent treatment,⁶⁷⁶ in line with other Brazilian and international guidelines, which set the cutoff point at 160 mm Hg.¹⁶⁴

When to initiate pharmacological treatment for pregnant hypertensives with BP below 160/110 mm Hg is still controversial, except for pregnant women with end-organ damage (EOD). Cochrane's systematic review⁶⁸⁵ showed that treating mild to moderate HT does not significantly lower maternal, fetal, and newborn morbidity.

However, the CHIPS trial,^{686,687} which assessed aggressive treatment (DBP up to 85 mm Hg) versus nonaggressive treatment (DBP up to 100 mm Hg) in a post-hoc analysis, found a major increase in severe hypertension and unfavorable fetal outcomes, such as miscarriages, ICU stays longer than 48 hours, preterm birth, and low weight. Thus, new studies are assessing whether to administer medication starting at 140/90 mm Hg.⁶⁶⁵

According to ACOG, the HT control target should be SBP > 120 and < 160 mm Hg, and DBP > 80 and < 110 mm Hg, since both hypertension and induced hypotension may harm placental perfusion and, consequently, fetal growth. The goal is to prevent the progression of EOD and cardiac

and cerebrovascular complications, as well as obstetric and fetal complications.⁶⁶⁵

Pharmacological therapy should begin as monotherapy using first-line medications (methyldopa, long-acting nifedipine, or beta-blockers, except atenolol). If proper control is not achieved, combine it with another first-line medication or a second-line one (thiazide diuretic, clonidine, and hydralazine); avoid combining medications from the same pharmacological class. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are formally contraindicated in case of pregnancy due to the risk of fetal malformation, which may lead to intrauterine renal failure, as are mineralocorticoid receptor antagonists, due to hormonal blockade, and atenolol, due to the high risk of fetal growth restriction associated with its use. Diuretics should also be avoided for PE patients due to the possibility of increasing intravascular volume depletion.^{665,688} A study comparing the efficacy of labetalol, long-acting nifedipine and methyldopa for managing severe gestational hypertension suggests that all medication classes were viable options, but long-acting nifedipine was more effective than labetalol and methyldopa.⁶⁸⁹

Hypertensive emergencies in pregnant women may be treated with oral nifedipine (10 mg) or with IV hydralazine. Currently, the trend is to prefer nifedipine 10 mg, which may be repeated in 10 to 20 mg orally every 20 to 30 minutes, and if patients are unresponsive after the third dose, 5 mg of IV hydralazine every 20 to 30 minutes up to a dose of 15 mg.⁶⁷⁴

In exceptional situations, such as acute pulmonary edema and refractory severe hypertension, the use of sodium nitroprusside may be considered the preferential option for urgent BP control⁶⁹⁰ for a maximum of 4 hours due to the risk of fetal cyanide poisoning.

In postpartum hypertension for nonchronic hypertensive patients, HT usually resolves within the 1st week (5 to 6 days), but the risk of complications such as stroke, acute pulmonary edema (APE), and renal failure remains during this period. There is also risk of eclampsia during this period, and 32 to 44% of women may have postpartum seizures.⁶⁹¹

Postpartum women may take all antihypertensive medications, and breastfeeding is the only limiting factor. Therefore, physicians should prioritize antihypertensives excreted in breast milk to a lesser extent.

Chart 11.3 lists the main antihypertensive medications available in Brazil in terms of breastfeeding.⁶⁹²⁻⁶⁹⁴ Hypertensive crises in postpartum women may be treated in the conventional manner. A study comparing captopril and clonidine for HT control (SBP $\geq$ 180 mm Hg and DBP $\geq$ 110 mm Hg) found no significant difference between the two, only a tendency for clonidine to perform better on the 3rd day postpartum.⁶⁹⁵ Both were considered safe and effective for treating hypertensive emergencies in postpartum women.⁶⁹⁶

11.8. Future Cardiovascular Risk

Hypertensive disorders of pregnancy are a marker of future risk (I: A), and a more careful and integrated approach should be adopted for these women in order to effectively prevent cardiovascular and kidney disease (LR: I, LE: C). Patients who develop any form of HT during pregnancy, especially with negative outcomes, such as preterm birth and early PE, experience a consistent increase in risk of future CVD and kidney disease.⁶⁹⁶⁻⁶⁹⁹ The risk of chronic hypertension is 3 to 4 times higher, while risk of stroke is 1.8 times higher. Likewise, the risk of coronary artery disease (CAD) doubles with age.^{696,697}

In a prospective study,⁶⁹⁸ gestational HT was associated with greater incidence of CAD (HR: 1.8; 95% CI: 1.3 to 2.6; $p < 0.001$), HF (HR: 1.7; 95% CI: 1.04 to 2.60; $p = 0.03$), aortic stenosis (HR: 2.9; 95% CI: 1.5 to 5.4; $p < 0.001$), and mitral insufficiency (HR: 5.0; 95% CI: 1.5 to 17.1; $p = 0.01$), showing a 30% global CV risk increase. Norwegian data show that PE is associated with a 3- to 15-fold increase in risk of stage 5 CKD.⁶⁹⁹ Hypertensive disorders of pregnancy are a marker of future risk, and a more careful and integrated approach should be adopted for these women in order to effectively prevent CVD and kidney disease.

Key Takeaways	
Classification	Pre-eclampsia, chronic hypertension, overlapping pre-eclampsia, and gestational hypertension.
Prevention	Calcium and acetylsalicylic acid for high-risk patients.
Nonpharmacological treatment	Should not be used for persistent SBP above 160 mm Hg for more than 15 minutes. Relative rest at hospital with monitoring for pre-eclampsia. Hospitalization of pregnant patients with severe HT.
Expectant management	Expectant management is suggested between the 34th and 37th gestational weeks for stable women, without clinical worsening or severe hypertension.
Pharmacological treatment	Urgent pharmacological treatment is indicated for severe hypertension and in the presence of warning signs. Pharmacological treatment should be initiated when BP is above 150-160/100-110 mm Hg, with the goal of keeping it in the 120-160/80-100 mm Hg range. The choice of the antihypertensive medication depends on the attending physician's experience and familiarity with the drug chosen and its side effects. Magnesium sulfate is recommended for eclampsia prevention and treatment.

Chart 11.1 – Definition and classification of hypertensive disorders in pregnancy

DEFINITIONS	
Gestational hypertension	SBP ≥ 140 mm Hg and/or DBP ≥ 90 mm Hg, or both, measured twice and at least two hours apart.
Severe gestational hypertension	SBP ≥ 160 mm Hg and/or DBP ≥ 110 mm Hg, or both, measured twice and at least two hours apart.
Proteinuria	Proteinuria ≥ 300 mg in 24 h, urine protein/creatinine ratio of 0.3 g/g of creatinine or ++ in reagent strips (quantification is ideal).
CLASSIFICATION	
Pre-eclampsia (with or without severe features)	SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg, or both, in general after 20 weeks of gestation and often with proteinuria*. In the absence of proteinuria, the diagnosis can be made in the presence of severe features: thrombocytopenia ($< 100\,000\,109/L$), creatinine > 1.1 mg/dL or 2x baseline creatinine, two-fold elevation in liver transaminases, APE, abdominal pain, visual symptoms or headaches, seizures, no alternative diagnoses.
Chronic hypertension	HT diagnosed or present before pregnancy or before 20th gestational week; or HT first diagnosed during pregnancy but that does not normalize after childbirth.
Chronic hypertension with overlapping pre-eclampsia	Pre-eclampsia in women with a history of HT before pregnancy or before the 20th gestational week.
Gestational hypertension	SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg, or both, in women with previously normal BP, after 20 gestational weeks, measured twice and at least 4 hours apart, without proteinuria or severe features, and returning to normal after childbirth.
OTHER DIAGNOSTIC DEFINITIONS	
Eclampsia	Tonic-clonic seizures in the absence of other causal conditions.
HELLP Syndrome	Hemolysis, elevated liver enzymes, and thrombocytopenia.
Posterior reversible encephalopathy syndrome (PRES) and reversible cerebral vasoconstriction syndrome	PRES with imaging abnormalities is established by the presence of vasogenic edema and hyperintensities in the posterior aspect of the brain in MNR, as well as association with visual disturbances, seizures, headaches, and sensory alterations. Reversible cerebral vasoconstriction syndrome is characterized by the narrowing of cerebral arteries with thunderclap headache or focal neurological signs.

APE: acute pulmonary edema; BP: blood pressure; DBP: diastolic blood pressure; HT: hypertension; PRES: posterior reversible encephalopathy syndrome; SBP: systolic blood pressure.

Guidelines

Chart 11.2 – Recommendations for ASA use in pre-eclampsia prevention

Risk	Risk factor	Recommendation
High	Prior PE with adverse fetal outcome Multiple gestation Chronic HT DM type 1 or 2 Kidney disease Autoimmune disorder (SLE/APS)	Low-dose acetylsalicylic acid is recommended for 1 or more of these criteria.
Moderate	Nulliparity Obesity (BMI ≥ 30 kg/m ²) Family history of PE (mother or sister) Age ≥ 35 years Poor obstetric history (SGA, preterm, low weight, more than ten years between pregnancies)	Consider using low-dose acetylsalicylic acid if patient has more than one risk factor.

APS: antiphospholipid antibody syndrome; BMI: body mass index; DM: diabetes mellitus; HT: hypertension; PE: pre-eclampsia; SGA: small for gestational age; SLE: systemic lupus erythematosus.

Chart 11.3 – Actions of medications on breastfeeding

Drugs	Excretion in breast milk	Breastfeeding
Nifedipine	Little excretion	Allowed
Amlodipine	Insufficient studies	Unclear (apparently safe)
Diltiazem, verapamil	Insufficient studies	Unclear (use other medication)
Clonidine	Increased excretion	Avoid
ACEI: enalapril, captopril	Little excretion	Allowed without restrictions Allowed Allowed
Lisinopril, ramipril	Insufficient studies	Unclear (apparently safe)
ARB: losartan, valsartan, candesartan, olmesartan, telmisartan	Insufficient studies	Unclear (use other medication)
Hydrochlorothiazide	Little excretion	Use low dosage (< 50 mg)
Chlorthalidone	Little excretion	Slow elimination in newborns – avoid. Use low dosage
Furosemide	Insufficient studies	May decrease breast milk supply. Use only in case of clinical need
Spironolactone	Little excretion	Allowed
Atenolol	Increased excretion	Avoid
Metoprolol	Little excretion	Allowed
Carvedilol	Insufficient studies	Unclear
Propranolol	Little excretion	Allowed
Bisoprolol	Insufficient studies	Unclear (apparently safe)
Hydralazine	Little excretion	Allowed
Methyldopa	Little excretion	Allowed

12. Hypertension in Children and Adolescents

12.1. Epidemiological Context and Importance of Hypertension in Pediatrics

The prevalence of high blood pressure (HBP) and hypertension (HT) in children and adolescents has increased in recent years. The current prevalence of HT in the pediatric age group ranges from 3% to 5%, while HBP is estimated at 10-15%.^{700,701} In children ages 7 to 12, HBP and HT prevalence rates are 4.7% and 1.9% respectively, and both are more prevalent among the obese.⁷⁰²

The Brazilian Study of Cardiovascular Risks in Adolescents (ERICA) evaluated 73399 Brazilian students ages 12 to 17. Total HBP prevalence in Brazil was 14.5%, and the highest rate was 29.3% for boys ages 15 to 17. The overall prevalence of HT was 9.6%, likewise highest among older children. The study found that 17.8% of prevalence rates for HT among adolescents is attributable to obesity.⁷⁰³

Pediatric HT is usually asymptomatic, but as many as 40% of hypertensive children have left ventricular hypertrophy (LVH) at their initial diagnosis. Though oligosymptomatic in childhood, LVH is a precursor to arrhythmias and HF in adults.⁷⁰⁴ Pediatric HT is also associated with the development of other changes to end-organs, such as increased carotid intima-media thickness, lower arterial distensibility, and retinal arteriolar narrowing. Blood pressure measurements from the age of 3 onwards are recommended, at least annually.⁷⁰⁵

12.2. Definition and Etiology

In children and adolescents, the definitions of HBP and HT are related to the normal distribution curve for blood pressure (BP) and their percentile distributions. The measurement uses auscultation, taking into consideration sex, age, and height percentile of the child.^{164,706,707}

In 2017, normative BP scores and HT diagnosis and management recommendations for pediatric HT, excluding overweight and obese children and adolescents, were changed.^{5,705} The term prehypertension has been replaced by HBP. The new recommendations, below, redefine HT staging for children and adolescents, simplify recommendations for preventive assessment in routine pediatric visits, structure the initial management of patients diagnosed with HBP or HT, and increase the importance of ABPM readings in diagnosis and management for pediatric HT.

Chart 12.1 presents up-to-date definitions of normal BP, high BP and stages 1 and 2 HT in children and adolescents by age, sex, and height percentile.⁷⁰⁵ The younger the child and the higher the BP, the greater the chance of secondary HT. Parenchymal and obstructive nephropathies and renal artery stenosis are responsible for approximately 60 to 90% of cases and can affect all age ranges. Endocrine disorders, such as excessive mineralocorticoid, corticoid or catecholamine secretion, thyroid diseases, and hypercalcemia associated with hyperparathyroidism, account for approximately 5% of cases. Coarctation of the aorta is diagnosed in 2% of cases, while 5% of cases are attributed to other etiologies, such as

adverse effects of vasoactive and immunosuppressant drugs, steroid abuse, central nervous system changes, and increased intracranial pressure.^{164,705-707}

Primary HT seems to be the most common form of HT in adolescents. It is most often associated with overweight, obesity, and family history of HT.

12.3. Diagnostic

12.3.1. BP Measurement Methods

Measuring BP in children is recommended at every clinical assessment. It should be measured annually in children and adolescents ≥ 3 years old, taking into consideration established measurement standards. For children under the age of 3, blood pressure measurements should be performed in certain situations. BP measurements should be repeated at every appointment under conditions, such as obesity, kidney disease, coarctation of the aorta, DM or chronic use of medications known to be associated with increased BP. Correctly measuring BP, following the standards established above, is a precondition for obtaining reliable readings and properly categorizing pediatric BP.^{176,705} Preferably, it should be measured in the right arm, with the patient lying down until the age of three, and, in older children, with the patient sitting down, their arms lying at heart level, using an adequately sized cuff. The air bag should be 80 to 100% as long as the arm circumference (AC) and at least 40% as wide as the AC. Blood pressure assessments should follow the procedures described in Chapter 3. Use the auscultatory method to check for audible Korotkoff sounds to 0 mm Hg. The point where sounds become muffled is considered for DBP (Korotkoff phase IV). During the first appointment, BP should be measured on the four limbs, and when measured on lower limbs (LLs), the patient should be placed in ventral decubitus position, using an appropriately-sized cuff on their thigh and placing the stethoscope on their popliteal artery. SBP at the LLs is usually 10 to 20% higher than BP measured at the brachial artery.¹⁶⁴ Charts 12.2 and 12.3 list normal BP, high BP and stages 1 and 2 HT by sex, age, and height percentile, adapted from Flynn et al., 2017.⁷⁰⁵ Some authors consider the oscillometric method adequate for initial screening in children and adolescents, which would justify developing tables using validated devices.^{708,709} In Brazil, Jardim et al. have developed a blood pressure reference curve for nonoverweight adolescents ages 12 to 17 using the oscillometric method.⁷¹⁰

The following clinical risk conditions determine the need for routine BP measurement for children $3 < \text{years old}$: preterm birth, very low birth weight, intrauterine growth restriction, history of stay at neonatal intensive care unit (ICU) or umbilical catheterization after birth, congenital heart disease with or without surgical repair, recurring urinary tract infections, hematuria or proteinuria, nephropathy, solid organ transplantation, oncological disorders or bone marrow transplantation, chronic use of medications known to increase BP, system disorders associated with HT (neurofibromatosis, tuberous sclerosis, sickle cell anemia, among others), and evidence of intracranial hypertension.⁷⁰⁵

The oscillometric method is recommended for measuring BP in newborns (NB). Normative BP values for the neonates 15 days old and older and gestational age after birth of 26 to 44 weeks can be found in Chart 12.4.⁷¹¹ Oscillometric devices, duly validated for pediatric age groups, may be used for initial BP assessments. If elevated BP is suspected from oscillometric readings, auscultation should be used to verify the finding. Pediatric HT diagnoses are based on confirming BP values $\geq$ 95th percentile in three different visits using auscultation.⁷⁰⁵ Chart 12.5 provides a simplified list of BP values suggesting the need for additional clinical assessments.^{705,711}

12.4. History-Taking

Detailed data on birth, growth and development, personal antecedents of kidney, urological, endocrine, heart and neurological diseases, and lifestyle should be collected, in addition to data on the use of medications and other substances that may cause BP alterations. In addition, family antecedents for HT, kidney disease, and other CVRFs should be carefully assessed. Children $\geq$ 6 years old do not require extensive screening for secondary causes of HT in the presence of positive family history of HT, overweight, or obesity, and/or their history or physical examination do not suggest secondary causes.^{705,712}

12.5. Physical Examination

On physical examination, the patient's body mass index (BMI) should be calculated⁷¹³ and the physician should investigate signs of secondary HT (see Chapter 15).⁷¹⁴

12.6. Additional tests

Laboratory and imaging tests are aimed at defining the etiology of HT (primary or secondary) and detecting end-organ damage (EOD) and cardiovascular risk factors (CVRFs) associated with HT (Charts 12.6 and 12.7).^{705,715} End-organ assessments should be performed in all children and adolescents with stages 1 and 2 HT. Sleep study by use of polysomnography is indicated for children and adolescents with sleep disorders detected while taking their histories.⁷⁰⁵

12.7. Ambulatory Blood Pressure Monitoring (ABPM)

ABPM should be used to confirm HT in children and adolescents with office BP readings compatible with high BP for at least a year or with BP readings corresponding to stage 1 HT in three outpatient visits.⁷⁰⁵ It should also be considered in routine examinations for secondary HT, CKD, diabetes mellitus (DM), obstructive sleep apnea (OSA), obesity, post-operative coarctation of the aorta, preterm birth, solid organ transplantation, and RfHT. The procedure should follow standard techniques and use monitors validated for pediatric use as well as pediatric reference data.⁷¹⁶

The 6th ABPM guidelines and 4th home blood pressure monitoring (HBPM) guidelines provide the information required to analyze ABPM data from children and adolescents.¹⁸⁶ BP categorization using ABPM data takes into account, in addition to BP readings, blood pressure load parameters, and BP dipping during nighttime sleep, as shown in Chart 12.7.⁷¹³

12.8. Therapeutic Aspects

The primary objectives of treating HT during childhood and adolescence is preventing EOD and continued HT in adulthood. The plan depends on the etiology of HT, cardiovascular (CV) risk associated with other underlying diseases, and the presence of EOD (LE: C).⁷⁰⁵

12.9. Nonpharmacological Therapy

Nonpharmacological therapy should be introduced to all pediatric patients with BP levels above the 90th percentile or BP $<$ 130/80 ($\geq$ 13 years old) (LE: C).⁷⁰⁵ This includes weight loss, physical exercise, dietary intervention, and stress control. The combination of these four measures leverages their impact compared to the individual effect of each intervention.⁷⁰⁵

Weight loss provides good results, and the use of a motivational approach seems to be the most effective method for controlling the association between obesity and HT in childhood (LE: C).⁷¹⁷ All children and adolescents should perform at least 300 minutes of moderate to vigorous physical activity per week for their health. In addition, sedentary behavior (time spent sitting or lying down) should be restricted for this age group. Structured physical exercise has greater impact on SBP values.⁷¹⁷ It is recommended that they perform moderate-intensity aerobic exercises (30-60 minutes) at least three times a week, and daily if possible.⁷⁰⁵ Resistance training can be added to this regimen. Competitive sports are not recommended for patients with uncontrolled stage 2 HT (LE: C).⁷¹⁸

Dietary interventions should include restricted sodium intake and may include potassium and calcium supplementation. Observational studies have shown the positive effects of the polyphenols found in olive oil.^{705,719} This guideline recommends the DASH diet, which emphasizes plant-based foods and decreased intake of sugar and sweets. This measure is especially effective for HT associated with obesity (LE: B).⁷¹⁹⁻⁷²¹ Stress control is also recommended for this age group, and may be achieved with various forms of meditation, mindfulness, and yoga (LE: C).⁷⁰⁵

12.10. Pharmacological Therapy

Pharmacological therapy should be initiated for children with symptomatic HT, secondary to CKD or DM, presence of EOD, stage 2 HT with no apparent modifiable cause, and persistent HT nonresponsive to lifestyle changes (LSCs) (LE: B).⁷⁰⁵ The treatment target is to lower BP below the 90th percentile (LE: C). Treatment should begin with an antihypertensive agent at its lowest dose, increased every two to four weeks until the target level is achieved. If this regimen is not sufficiently effective, other medication classes are added in sequence. Since many medication classes increase sodium and fluid retention, considering thiazide diuretics is recommended as the second medication for combination therapies. Overall, adverse events associated with the use of antihypertensive agents in children and adolescents have been mild (LE: B).^{705,722}

All classes of antihypertensive drugs seem safe, at least in the short run.⁷²² However, recent international guidelines recommend preferential use of angiotensin-converting enzyme inhibitors (ACEIs), ARBs, long-acting CCBs, or thiazide

DIUs as first-line medications. If a third antihypertensive is needed, the recommended medications are alpha-blockers, BBs, centrally acting sympatholytics, or potassium-sparing diuretics (LE: C).^{705,722}

In secondary HT, the choice of antihypertensive should follow the physiopathological principle involved, taking into account the comorbidities present in each case.⁷¹⁹⁻⁷²⁶ Patients with resistant HT require stronger decreases in sodium intake, as well as detailed investigation of their consumption of substances or foods causing HT, adherence to therapy regimen, and maximum optimization of said regimen (LE: C).⁷⁰⁵

If the patient does not respond to monotherapy for longer than six months, their referral to a specialist in HT in children and adolescents should be considered (LE: C).⁷²⁷ Chart 12.8 provides a list of medications used in pediatric settings and their dosage.^{705,725,726}

12.11. Follow-up of Children and Adolescents with HT

Frequency of follow-up in children and adolescents with HT depends on severity and need for treatment. Patients undergoing nonpharmacological therapy only should have clinical follow-up visits every 3 to 6 months, with HBPM as an adjuvant for blood pressure control.

For patients requiring medications, soon after treatment onset, follow-up visits should be scheduled every 15 to 30 days after establishing the optimum dose or need for combination. In an intermediate stage, visits should be scheduled every 4 to 6 weeks, and quarterly once HT is controlled.

Follow-up appointments should include a detailed analysis of adherence and side effects. Requesting laboratory

tests depends on the medications used and severity of HT and underlying diseases; likewise, how frequently the patient is tested for EOD depends on the underlying disease and on the severity of HT. Requesting ABPM is indicated when there is no HT control or when there is risk of masked hypertension (MH), such as the late post-operative period after surgical correction for coarctation of the aorta (LE: C).⁷⁰⁵

12.12. Hypertensive Crisis

Hypertensive emergencies (HEs) and hypertensive urgencies (HUs) are defined in Chapter 13.⁷²⁷ There is no consensus BP level that defines HE,⁷²⁸ though some authors suggest a cutoff point 20% above stage 2 HT (> 99th percentile).⁷²⁹ The American Academy of Pediatrics (AAP), in turn, defines HE as any condition in which a child has BP above stage 2 HT. However, the AAP warns that children with BP > 95th percentile + 30 mm Hg run a higher risk of complications. In general, HEs are secondary to underlying diseases still requiring investigation,⁷⁰⁵ and most often should be treated with intravenous (IV) medication administered to hospitalized patients, often in the ICU. Patients with HUs and no signs of end-organ impairment may initially receive central alpha-agonists, vasodilators or CCBs.⁷⁰⁵ The objective of treatment is to lower BP by 25% during the first 8 hours, followed by a slow decrease over 24 to 48 hours, until reaching the 95th percentile, since accelerated decreases may cause damage, especially to the brain.^{730,731} Chart 12.9 shows the most frequently used medications in pediatric HEs (LE: C).13. Crise Hipertensiva

Key Takeaways

All children and adolescents ≥ 3 years old should have their BP measured annually.

Children 3 < years old should undergo BP measurements in case of preterm birth, very low birth weight, intrauterine growth restriction, history of stay at neonatal ICU, congenital heart disease, nephropathy, solid organ transplantation, oncological disorders, chronic use of medications known to increase BP, system disorders associated with HT, and evidence of intracranial hypertension.

All children and adolescents ≥ 3 years old should have their BP measured at every medical visit in case of overweight, chronic use of medications known to increase BP, kidney disease, coarctation of the aorta, and diabetes.

Children and adolescents should be diagnosed with HT when BP measured by auscultation in three separate visits is above the 95th percentile for their age, sex, and height percentile.

In children and adolescents diagnosed with HT, the pharmacological and nonpharmacological treatment goals should be to lower BP to below the 90th percentile for age, sex, and height percentile and to < 130/80 mm Hg in adolescents ≥ 13 years old.

Guidelines

Quadro 12.1 – Definição atualizada da pressão arterial de acordo com a faixa etária

Crianças de 1 a 13 anos de idade	Crianças com idade ≥13 anos
PA normal: < P90 para idade, sexo e altura	PA normal: < 120 / < 80 mm Hg
Pressão arterial elevada: PA ≥ P90 e < 95 percentil para idade, sexo e altura ou PA 120/80 mmHg mas < P95 (o que for menor)	Pressão arterial elevada: PA120 / <80 mmHg a PA129 / <80 mm Hg
Hipertensão estágio 1: PA ≥ P95 para idade, sexo e altura até < P95 + 12 mmHg ou PA entre 130/80 até 139/89mmHg (o que for menor)	Hipertensão estágio 1: PA 130/80 ou até 139/89 mm Hg
Hipertensão estágio 2: PA ≥ P95 + 12 mmHg para idade, sexo e altura ou PA ≥ 140/90 mmHg (o que for menor)	Hipertensão estágio 2: PA ≥ 140/90mmHg

PA: pressão arterial; P: percentil.
Adaptado de Flynn et al., 2017.⁷⁰⁵

Chart 12.1 – Updated definition of blood pressure according to age group.

Children 1 to 13 years old	Children ages ≥13 years old
Normal BP: < P90 for age, sex, and height	Normal BP: < 120 / < 80 mm Hg
High blood pressure: BP ≥ P90 and < 95th percentile for age, sex, and height or BP 120/80 mm Hg but < P95 (whichever is lowest)	High blood pressure: BP 120 / <80 mm Hg to PA129 / <80 mm Hg
Stage 1 hypertension: BP ≥ P95 for age, sex, and height up to < P95 + 12 mm Hg or BP between 130/80 and 139/89mm Hg (whichever is lowest)	Stage 1 hypertension: BP 130/80 or up to 139/89 mm Hg
Stage 2 hypertension: BP ≥ P95 + 12 mm Hg or age, sex and height or BP ≥ 140/90 mm Hg (whichever is lowest)	Stage 2 hypertension: BP ≥ 140/90 mm Hg

BP: blood pressure; P: percentile.
Adapted from Flynn et al., 2017.⁷⁰⁵

Chart 12.2 – Blood pressure levels for boys by age and height percentile

Age (years)	BP percentiles	Systolic blood pressure (mm Hg) Height percentiles or height measurement (cm)							Diastolic blood pressure (mm Hg) Height percentiles or height measurement (cm)						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	Height (cm)	77.2	78.3	80.2	82.4	84.6	86.7	87.9	77.2	78.3	80.2	82.4	84.6	86.7	87.9
	P50	85	85	86	86	87	88	88	40	40	40	41	41	42	42
	P90	98	99	99	100	100	101	101	52	52	53	53	54	54	54
	P95	102	102	103	103	104	105	105	54	54	55	55	56	57	57
	P95 + 12 mmHg	114	114	115	115	116	117	117	66	66	67	67	68	69	69
2	Height (cm)	86.1	87.4	89.6	92.1	94.7	97.1	98.5	86.1	87.4	89.6	92.1	94.7	97.1	98.5
	P50	87	87	88	89	89	90	91	43	43	44	44	45	46	46
	P90	100	100	101	102	103	103	104	55	55	56	56	57	58	58
	P95	104	105	105	106	107	107	108	57	58	58	59	60	61	61
	P95 + 12 mmHg	116	117	117	118	119	119	120	69	70	70	71	72	73	73
3	Height (cm)	92.5	93.9	96.3	99	101.8	104.3	105.8	92.5	93.9	96.3	99	101.8	104.3	105.8
	P50	88	89	89	90	91	92	92	45	46	46	47	48	49	49
	P90	101	102	102	103	104	105	105	58	58	59	59	60	61	61
	P95	106	106	107	107	108	109	109	60	61	61	62	63	64	64
	P95 + 12 mmHg	118	118	119	119	120	121	121	72	73	73	74	75	76	76
4	Height (cm)	98.5	100.2	102.9	105.9	108.9	111.5	113.2	98.5	100.2	102.9	105.9	108.9	111.5	113.2
	P50	90	90	91	92	93	94	94	48	49	49	50	51	52	52
	P90	102	103	104	105	105	106	107	60	61	62	62	63	64	64
	P95	107	107	108	108	109	110	110	63	64	65	66	67	67	68
	P95 + 12 mmHg	119	119	120	120	121	122	122	75	76	77	78	79	79	80
5	Height (cm)	104.4	106.2	109.1	112.4	115.7	118.6	120.3	104.4	106.2	109.1	112.4	115.7	118.6	120.3
	P50	91	92	93	94	95	96	96	51	51	52	53	54	55	55
	P90	103	104	105	106	107	108	108	63	64	65	65	66	67	67
	P95	107	108	109	109	110	111	112	66	67	68	69	70	70	71
	P95 + 12 mmHg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
6	Height (cm)	110.3	112.2	115.3	118.9	122.4	125.6	127.5	110.3	112.2	115.3	118.9	122.4	125.6	127.5
	P50	93	93	94	95	96	97	98	54	54	55	56	57	57	58
	P90	105	105	106	107	109	110	110	66	66	67	68	68	69	69
	P95	108	109	110	111	112	113	114	69	70	70	71	72	72	73
	P95 + 12 mmHg	120	121	122	123	124	125	126	81	82	82	83	84	84	85
7	Height (cm)	116.1	118	121.4	125.1	128.9	132.4	134.5	116.1	118	121.4	125.1	128.9	132.4	134.5
	P50	94	94	95	97	98	98	99	56	56	57	58	58	59	59
	P90	106	107	108	109	110	111	111	68	68	69	70	70	71	71
	P95	110	110	111	112	114	115	116	71	71	72	73	73	74	74
	P95 + 12 mmHg	122	122	123	124	126	127	128	83	83	84	85	85	86	86
8	Height (cm)	121.4	123.5	127	131	135.1	138.8	141	121.4	123.5	127	131	135.1	138.8	141
	P50	95	96	97	98	99	99	100	57	57	58	59	59	60	60
	P90	107	108	109	110	111	112	112	69	70	70	71	72	72	73
	P95	111	112	112	114	115	116	117	72	73	73	74	75	75	75
	P95 + 12 mmHg	123	124	124	126	127	128	129	84	85	85	86	87	87	87
9	Height (cm)	126	128.3	132.1	136.3	140.7	144.7	147.1	126	128.3	132.1	136.3	140.7	144.7	147.1
	P50	96	97	98	99	100	101	101	57	58	59	60	61	62	62
	P90	107	108	109	110	112	113	114	70	71	72	73	74	74	74
	P95	112	112	113	115	116	118	119	74	74	75	76	76	77	77
	P95 + 12 mmHg	124	124	125	127	128	130	131	86	86	87	88	88	89	89

Guidelines

Age (years)	BP percentiles	Systolic blood pressure (mm Hg) Height percentiles or height measurement (cm)							Diastolic blood pressure (mm Hg) Height percentiles or height measurement (cm)						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
10	Height (cm)	130.2	132.7	136.7	141.3	145.9	150.1	152.7	130.2	132.7	136.7	141.3	142.9	150.1	152.7
	P50	97	98	99	100	101	102	103	59	60	61	62	63	63	64
	P90	108	109	111	112	113	115	116	72	73	74	74	75	75	76
	P95	112	113	114	116	118	120	121	76	76	77	77	78	78	78
	P95 + 12 mmHg	124	125	126	128	130	132	133	88	88	89	89	90	90	90
11	Height (cm)	134.7	137.3	141.5	146.4	151.3	155.8	158.6	134.7	137.3	141.5	146.4	151.3	155.8	158.6
	P50	99	99	101	102	103	104	106	61	61	62	63	63	63	63
	P90	110	111	112	114	116	117	118	74	74	75	75	75	76	76
	P95	114	114	116	118	120	123	124	77	78	78	78	78	78	78
	P95 + 12 mmHg	126	126	128	130	132	135	136	89	90	90	90	90	90	90
12	Height (cm)	140.3	143	147.5	152.7	157.9	162.6	165.5	140.3	143	147.5	152.7	157.9	162.6	165.5
	P50	101	101	102	104	106	108	109	61	62	62	62	62	63	63
	P90	113	114	115	117	119	121	122	75	75	75	75	75	76	76
	P95	116	117	118	121	124	126	128	78	78	78	78	78	79	79
	P95 + 12 mmHg	128	129	130	133	136	138	140	90	90	90	90	90	91	91
13	Height (cm)	147	150	154.9	160.3	165.7	170.5	173.4	147	150	154.9	160.3	165.7	170.5	173.4
	P50	103	104	105	108	110	111	112	61	60	61	62	63	64	65
	P90	115	116	118	121	124	126	126	74	74	74	75	76	77	77
	P95	119	120	122	125	128	130	131	78	78	78	78	80	81	81
	P95 + 12 mmHg	131	132	134	137	140	142	143	90	90	90	90	92	93	93
14	Height (cm)	153.8	156.9	162	167.5	172.7	177.4	180.1	153.8	156.9	162	167.5	172.7	177.4	180.1
	P50	105	106	109	111	112	113	113	60	60	62	64	65	66	67
	P90	119	120	123	126	127	128	129	74	74	75	77	78	79	80
	P95	123	125	127	130	132	133	134	77	78	79	81	82	83	84
	P95 + 12 mmHg	135	137	139	142	144	145	146	89	90	91	93	94	95	96
15	Height (cm)	159	162	166.9	172.2	177.2	181.6	184.2	159	162	166.9	172.2	177.2	181.6	184.2
	P50	108	110	112	113	114	114	114	61	62	64	65	66	67	68
	P90	123	124	126	128	129	130	130	75	76	78	79	80	81	81
	P95	127	129	131	132	134	135	135	78	79	81	83	84	85	85
	P95 + 12 mmHg	139	141	143	144	146	147	147	90	91	93	95	96	97	97
16	Height (cm)	162.1	165	169.6	174.6	179.5	183.8	186.4	162.1	165	169.6	174.6	179.5	183.8	186.4
	P50	111	112	114	115	115	116	116	63	64	66	67	68	69	69
	P90	126	127	128	129	131	131	132	77	78	79	80	81	82	82
	P95	130	131	133	134	135	136	137	80	81	83	84	85	86	86
	P95 + 12 mmHg	142	143	145	146	147	148	149	92	93	95	96	97	98	98
17	Height (cm)	163.8	166.5	170.9	175.8	180.7	184.9	187.5	163.8	166.5	170.9	175.8	180.7	184.9	187.5
	P50	114	115	116	117	117	118	118	65	66	67	68	69	70	70
	P90	128	129	130	131	132	133	134	78	79	80	81	82	82	83
	P95	132	133	134	135	137	138	138	81	82	84	85	86	86	87
	P95 + 12 mmHg	144	145	146	147	149	150	150	93	94	96	97	98	98	99

Adapted from Flynn et al., 2017.⁷⁰⁵

Chart 12.3 – Blood pressure levels for girls by age and height percentile

Age (years)	BP percentiles	Systolic blood pressure (mm Hg) Height percentiles or height measurement (cm)							Diastolic blood pressure (mm Hg) Height percentiles or height measurement (cm)						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
1	Height (cm)	75.4	76.6	78.6	80.8	83	84.9	86.1	75.4	76.6	78.6	80.8	83	84.9	86.1
	P50	84	85	86	86	87	88	88	41	42	42	43	44	45	46
	P90	98	99	99	100	101	102	102	54	55	56	56	57	58	58
	P95	101	102	102	103	104	105	105	59	59	60	60	61	62	62
	P95 + 12 mmHg	113	114	114	115	116	117	117	71	71	72	72	73	74	74
2	Height (cm)	84.9	86.3	88.6	91.1	93.7	96	97.4	84.9	86.3	88.6	91.1	93.7	96	97.4
	P50	87	87	88	89	90	91	91	45	46	47	48	49	50	51
	P90	101	101	102	103	104	105	106	58	58	59	60	61	62	62
	P95	104	105	106	106	107	108	109	62	63	63	64	65	66	66
	P95 + 12 mmHg	116	117	118	118	119	120	121	74	75	75	76	77	78	78
3	Height (cm)	91	92.4	94.9	97.6	100.5	103.1	104.6	91	92.4	94.9	97.6	100.5	103.1	104.6
	P50	88	89	89	90	91	92	93	48	48	49	50	51	53	53
	P90	102	103	104	104	105	106	107	60	61	61	62	63	64	65
	P95	106	106	107	108	109	110	110	64	65	65	66	67	68	69
	P95 + 12 mmHg	118	118	119	120	121	122	122	76	77	77	78	79	80	81
4	Height (cm)	97.2	98.8	101.4	104.5	107.6	110.5	112.2	97.2	98.8	101.4	104.5	107.6	110.5	112.2
	P50	89	90	91	92	93	94	94	50	51	51	53	54	55	55
	P90	103	104	105	106	107	108	108	62	63	64	65	66	67	67
	P95	107	108	109	109	110	111	112	66	67	68	69	70	70	71
	P95 + 12 mmHg	119	120	121	121	122	123	124	78	79	80	81	82	82	83
5	Height (cm)	103.6	105.3	108.2	111.5	114.9	118.1	120	103.6	105.3	108.2	111.5	114.9	118.1	120
	P50	90	91	92	93	94	95	96	52	52	53	55	56	57	57
	P90	104	105	106	107	108	109	110	64	65	66	67	68	69	70
	P95	108	109	109	110	111	112	113	68	69	70	71	72	73	73
	P95 + 12 mmHg	120	121	121	122	123	124	125	80	81	82	83	84	85	85
6	Height (cm)	110	111.8	114.9	118.4	122.1	125.6	127.7	110	111.8	114.9	118.4	122.1	125.6	127.7
	P50	92	92	93	94	96	97	97	54	54	55	56	57	58	59
	P90	105	106	107	108	109	110	111	67	67	68	69	70	71	71
	P95	109	109	110	111	112	113	114	70	71	72	72	73	74	74
	P95 + 12 mmHg	121	121	122	123	124	125	126	82	83	84	84	85	86	86
7	Height (cm)	115.9	117.8	121.1	124.9	128.8	132.5	134.7	115.9	117.8	121.1	124.9	128.8	132.5	134.7
	P50	92	93	94	95	97	98	99	55	55	56	57	58	59	60
	P90	106	106	107	109	110	111	112	68	68	69	70	71	72	72
	P95	109	110	111	112	113	114	115	72	72	73	73	74	74	75
	P95 + 12 mmHg	121	122	123	124	125	126	127	84	84	85	85	86	86	87
8	Height (cm)	121	123	126.5	130.6	134.7	138.5	140.9	121	123	126.5	130.6	134.7	138.5	140.9
	P50	93	94	95	97	98	99	100	56	56	57	59	60	61	61
	P90	107	107	108	110	111	112	113	69	70	71	72	72	73	73
	P95	110	111	112	113	115	116	117	72	73	74	74	75	75	75
	P95 + 12 mmHg	122	123	124	125	127	128	129	84	85	86	86	87	87	87
9	Height (cm)	125.3	127.6	131.3	135.6	140.1	144.1	146.6	125.3	127.6	131.3	135.6	140.1	144.1	146.6
	P50	95	95	97	98	99	100	101	57	58	59	60	60	61	61
	P90	108	108	109	111	112	113	114	71	71	72	73	73	73	73
	P95	112	112	113	114	116	117	118	74	74	75	75	75	75	75
	P95 + 12 mmHg	124	124	125	126	128	129	130	86	86	87	87	87	87	87

Guidelines

Age (years)	BP percentiles	Systolic blood pressure (mm Hg) Height percentiles or height measurement (cm)							Diastolic blood pressure (mm Hg) Height percentiles or height measurement (cm)						
		5%	10%	25%	50%	75%	90%	95%	5%	10%	25%	50%	75%	90%	95%
10	Height (cm)	129.7	132.2	136.3	141	145.8	150.2	152.8	129.7	132.2	136.3	141	145.8	150.2	152.8
	P50	96	97	98	99	101	102	103	58	59	59	60	61	61	61
	P90	109	110	111	112	113	115	116	72	73	73	73	73	73	73
	P95	113	114	114	116	117	119	120	75	75	76	76	76	76	76
	P95 + 12 mmHg	125	126	126	128	129	131	132	87	87	88	88	88	88	88
11	Height (cm)	135.6	138.3	142.8	147.8	152.8	157.3	160	135.6	138.3	142.8	147.8	152.8	157.3	160
	P50	98	99	101	102	104	105	106	60	60	60	61	62	63	64
	P90	111	112	113	114	116	118	120	74	74	74	74	74	75	75
	P95	115	116	117	118	120	123	124	76	77	77	77	77	77	77
	P95 + 12 mmHg	127	128	129	130	132	135	136	88	89	89	89	89	89	89
12	Height (cm)	142.8	145.5	149.9	154.8	159.6	163.8	166.4	142.8	145.5	149.9	154.8	159.6	163.8	166.4
	P50	102	102	104	105	107	108	108	61	61	61	62	64	65	65
	P90	114	115	116	118	120	122	122	75	75	75	75	76	76	76
	P95	118	119	120	122	124	125	126	78	78	78	78	79	79	79
	P95 + 12 mmHg	130	131	132	134	136	137	138	90	90	90	90	91	91	91
13	Height (cm)	148.1	150.6	154.7	159.2	163.7	167.8	170.2	148.1	150.6	154.7	159.2	163.7	167.8	170.2
	P50	104	105	106	107	108	108	109	62	62	63	64	65	65	65
	P90	116	117	119	121	122	123	123	75	75	75	76	76	76	76
	P95	121	122	123	124	126	126	127	79	79	79	79	80	80	81
	P95 + 12 mmHg	133	134	135	136	138	138	139	91	91	91	91	92	92	93
14	Height (cm)	150.6	153	156.9	161.3	165.7	169.7	172.1	150.6	153	156.9	161.3	165.7	169.7	172.1
	P50	105	106	107	108	109	109	109	63	63	64	65	66	66	66
	P90	118	118	120	122	123	123	123	76	76	76	76	77	77	77
	P95	123	123	124	125	126	127	127	80	80	80	80	81	81	82
	P95 + 12 mmHg	135	135	136	137	138	139	139	92	92	92	92	93	93	94
15	Height (cm)	151.7	154	157.9	162.3	166.7	170.6	173	151.7	154	157.9	162.3	166.7	170.6	173
	P50	105	106	107	108	109	109	109	64	64	64	65	66	67	67
	P90	118	119	121	122	123	123	124	76	76	76	77	77	78	78
	P95	124	124	125	126	127	127	128	80	80	80	81	82	82	82
	P95 + 12 mmHg	136	136	137	138	139	139	140	92	92	92	93	94	94	94
16	Height (cm)	152.1	154.5	158.4	162.8	167.1	171.1	173.4	152.1	154.5	158.4	162.8	167.1	171.1	173.4
	P50	106	107	108	109	109	110	110	64	64	65	66	66	67	67
	P90	119	120	122	123	124	124	124	76	76	76	77	78	78	78
	P95	124	125	125	127	127	128	128	80	80	80	81	82	82	82
	P95 + 12 mmHg	136	137	137	139	139	140	140	92	92	92	93	94	94	94
17	Height (cm)	152.4	154.7	158.7	163	167.4	171.3	173.7	152.4	154.7	158.7	163	167.4	171.3	173.7
	P50	107	108	109	110	110	110	111	64	64	65	66	66	66	67
	P90	120	121	123	124	124	125	125	76	76	77	77	78	78	78
	P95	125	125	126	127	128	128	128	80	80	80	81	82	82	82
	P95 + 12 mmHg	137	137	138	139	140	140	140	92	92	92	93	94	94	94

Adapted from Flynn et al, 2017.⁷⁰⁵

Chart 12.4 – Estimated blood pressure levels at two weeks for neonates 26 to 44 weeks since conception.

Age since conception	50th Percentile	95th Percentile	99th Percentile
44 weeks			
SBP	88	105	110
DBP	50	68	73
MAP	63	80	85
42 weeks			
SBP	85	98	102
DBP	50	65	70
MAP	62	76	81
40 weeks			
SBP	80	95	100
DBP	50	65	70
MAP	60	75	80
38 weeks			
SBP	77	92	97
DBP	50	65	70
MAP	59	74	79
36 weeks			
SBP	72	87	92
DBP	50	65	70
MAP	57	72	71
34 weeks			
SBP	70	85	90
DBP	40	55	60
MAP	50	65	70
32 weeks			
SBP	68	83	88
DBP	40	55	60
MAP	50	65	70
30 weeks			
SBP	65	80	85
DBP	40	55	60
MAP	48	65	68
28 weeks			
SBP	60	75	80
DBP	38	50	54
MAP	45	58	63
26 weeks			
SBP	55	72	77
DBP	30	50	56
MAP	38	57	63

DBP: diastolic blood pressure; MAP: mean arterial pressure; SBP: systolic blood pressure. Adapted from Dionne et al., 2012.⁷¹¹

Chart 12.5 – BP values considered warning signs for additional clinical assessment by chronological age

Age	Male		Female	
	SBP	DBP	SBP	DBP
1	98	52	98	54
2	100	55	101	58
3	101	58	102	60
4	102	60	103	62
5	103	63	104	64
6	105	66	105	67
7	106	68	106	68
8	107	69	107	69
9	107	70	108	71
10	108	72	109	72
11	110	74	111	74
12	113	75	114	75
≥13	120	80	120	80

DBP: diastolic blood pressure; SBP: systolic blood pressure.
Adapted from Flynn et al., 2017.⁷⁰⁵

Chart 12.6 – Initial investigation in children and adolescents with HT.

Complete blood count
Kidney function and electrolytes (including calcium, phosphorus and magnesium)
Lipid profile
Serum uric acid
Fasting glycemia
Urinalysis and urine culture
Fundoscopy
Chest X-ray
Doppler echocardiography
Kidney and urinary tract ultrasound and Doppler ultrasound of renal arteries

US: ultrasound.

Guidelines

Chart 12.7 – Suggested ambulatory BP staging in children and adolescents

Classification	Office BP	Ambulatory SBP/DBP	Systolic/diastolic load
Normal BP	< P90	< P95	<25%
White-coat hypertension	≥ P95	< P95	<25%
High BP	≥ P90 or > 120/80 mm Hg	< P 95	≥ 25%
Masked hypertension	< P95	< P95	≥ 25%
Ambulatory hypertension	> P95	> P95 (> P90 secondary HT)	25 to 50%
Severe ambulatory hypertension	>P95	> P95	> 50%

BP: blood pressure; P: percentile. Adapted from Flynn et al., 2017.⁷⁰⁵

Chart 12.8 – Antihypertensive medications prescribed to children and adolescents in Brazil

Medication	Age	Initial dose	Maximum dose	Interval
Clonidine	> 12 to	0.2 mg/day	2.4 mg/day	12 h
Atenolol		0.5-1 mg/kg/dose	2 mg/kg/day (max. 100 mg/day)	12-24 h
Propranolol		1-2 mg/kg/dose	4 mg/kg/day (max. 640 mg/day)	8-12 h
Amlodipine	1-5 years	0.1 mg/kg/dose	0.6 mg/kg/day (max. 5 mg/day)	24 h
	> 6 years	2.5 mg/day	10 mg/day	24 h
Isradipine	Toddler	0.05-0.1 mg/kg/dose	0.6 mg/kg/day (max. 10 mg/day)	8-12 h
Felodipine	> 6 years	2.5 mg/day	10 mg/day	24 h
Nifedipine XL		0.25-0.5 mg/kg/dose	3 mg/kg/day (max. 120 mg/day)	12-24 h
Candesartan	1-5 years	0.02 mg/kg/dose (max. 4 mg/day)	0.4 mg/kg/day (max. 16 mg/day)	12-24 h
Olmesartan	> 6 years	< 35 kg: 10 mg/day	< 35 kg: 20 mg/day	24 h
		> 35 kg: 20 mg/day	> 35 kg: 40 mg/day	24 h
Losartan	> 6 years	0.7 mg/kg/day (max. 50 mg/day)	1.4 mg/kg/day (max. 100 mg/day)	24 h
Valsartan	> 6 years	1.3 mg/kg/day	2.7 mg/kg/day (max. 160 mg/day)	24 h
Prazosine	> 12 years	0.05-0.1 mg/kg/dose	0.5 mg/kg/day	8 h
Furosemide		0.5-2 mg/kg/dose	6 mg/kg/day	4-12 h
Spironolactone		1 mg/kg/dose	3.3 mg/kg/day (100 mg/day)	6-12 h
Chlorthalidone	> 40 kg	0.3 (max. 50 mg/day)	2 mg/kg/day	24 h
Hydrochlorothiazide		1 mg/kg/dose	2 mg/kg/day (max. 37.5 mg/day)	
Benazepril	> 6 years	0.2 (max. 10 mg/day)	0.6 mg/kg/day (max. 40 mg/day)	24 h
Captopril	Infant	0.05 mg/kg/dose	6 mg/kg/day	6-24 h
	Toddler	0.5 mg/kg/dose	6 mg/kg/day	8 h
Enalapril	> 1 month	0.08 mg/kg/dose	0.6 mg/kg/day (max. 40 mg/day)	12-24 h
Fosinopril	> 6 years	0.2 mg/kg/dose (max. 10 mg/day)	0.6 mg/kg/day (max. 40 mg/day)	24 h
Lisinopril	> 6 years	0.07 mg/kg/dose (max. 5 mg/day)	0.6 mg/kg/day (max. 40 mg/day)	24 h
Ramipril		1.6 mg/m2/day	6 mg/m2/day	24 h
Hydralazine		0.75 mg/kg/dose	7.5 mg/kg/day (max. 200 mg/day)	6 h
Minoxidil	< 12 years	0.2 mg/kg/dose	50 mg/day	6-8 h
	> 12 years	5 mg/day	100 mg/day	

h: hours; Max.: maximum.

Chart 12.9 – Major pediatric medications and doses used to control hypertensive emergencies

Medication	Route	Dose	Beginning of action	Duration
Sodium nitroprusside	IV	0.5-10 µg/kg/min	Seconds	Only during infusion
Labetalol	IV	0.25-3 mg/kg/h or bolus 0.2-1 mg/kg followed by infusion of 0.25-3 mg/kg/h	2-5 min	2-4 h
Nicardipine	IV	1-3 µg/kg/min	2-5 min	30 min-4 h, the greater, the longer the use
Hydralazine	IV IM	Bolus 0.2-0.6 mg/kg IV or IM, max. = 20mg	10-30 min	4-12 h
Esmolol	IV	Attack 100-500 µg/kg followed by infusion 50-300 µg/kg/min	Seconds	10-30 min
Phentolamine	IV	Bolus 0.05-0.1 mg/kg max. = 5 mg/dose	Seconds	15-20 min

h: hour; IM: intramuscular; IV: intravenous; min: minute. Adapted from Flynn et al., 2017.⁷⁰⁵

13. Hypertensive Crisis

13.1. Definition

The terms hypertensive urgency and hypertensive emergency were proposed as an operational classification of hypertensive crises (HCs) in 1993 by the V Joint National Committee on Detection Evaluation and Treatment of High Blood Pressure.⁷³²

Hypertensive urgencies (HUs) are symptomatic clinical situations in which there is significant blood pressure (BP) elevation (arbitrarily defined as systolic BP (SBP) DBP ≥ 180 mm Hg and/or diastolic BP (DBP) ≥ 120 mm Hg) without acute and progressive end-organ damage (EOD) and no imminent risk of death.^{5,164,733,734}

Hypertensive emergencies (HEs), in turn, are symptomatic clinical situations in which there is significant BP elevation (arbitrarily defined as SBP ≥ 180 mm Hg and/or DBP ≥ 120 mm Hg) with acute and progressive EOD and imminent risk of death.^{5,164,733,734}

A common condition at emergency rooms is the hypertensive pseudocrisis (HTPC). In HTPCs, there is no acute EOD or immediate risk of death. In general, it is seen in uncontrolled hypertensive patients undergoing treatment, or in untreated hypertensive patients, with very high BP measurements, but who are either oligosymptomatic or asymptomatic. High BP after an emotional, painful or uncomfortable event, such as migraines, dizziness, vascular and musculoskeletal headaches and panic attacks also characterize HTPC.^{733,734}

13.2. Classification

HE is not defined by BP level, though it is often very high, but predominantly by the patient's clinical status. It can manifest as a cardiovascular, cerebrovascular, renal, or multi-organ event, or even as pre-eclampsia with severe features or eclampsia. Chart 13.1 shows the classification of HEs. Chart 13.2 differentiates HUs from HEs in terms of diagnosis, prognosis, and management.

13.3. Major Epidemiological, Pathophysiological, and Prognostic Aspects

13.3.1. Epidemiology

Hypertensive crises account for 0.45 to 0.59% of all hospital emergency treatments, while HEs account for 25% of all cases of HC. Ischemic stroke and acute pulmonary edema (APE) are the most common conditions found in HEs⁷³⁵⁻⁷³⁷, with decreasing incidence in recent decades.⁷³⁸⁻⁷⁴⁰

13.3.2. Pathophysiology

Since systemic BP is the product of cardiac output (CO) by peripheral vascular resistance (PVR), acute increases in BP may be the result of changes to those variables. Therefore, increased intravascular volume and PVR, reduced production of endogenous vasodilators, and/or activation of vasoconstrictor systems may precipitate greater vascular reactivity, resulting in HC.^{741,742} Tissue autoregulation is compromised, particularly in the cerebral and renal vascular beds, resulting in local ischemia, which triggers a vicious circle of vasoconstriction, endothelial damage and activation of the platelet, coagulation and immune system, with myointimal proliferation, arteriole fibrinoid necrosis, and end-organ ischemia.⁷⁴¹⁻⁷⁴³ The autoregulation curve shifts to the right in chronic hypertensive patients, making both actual BP level and rate of increase important to the genesis of HE. On the other hand, that shift in the autoregulation curve predisposes patients to tissue ischemia in aggressive BP reductions in HE treatment.^{742,743}

13.3.3. Prognosis

The one-year mortality rate for untreated HE is approximately 80%,⁷³⁹ and effective antihypertensive treatment is associated with significant improvements in prognosis.⁷⁴⁰ Five-year survival rates are higher for individuals with HU than those with HE.^{735,744}

13.4. Complementary Clinical and Laboratory Investigation^{164,733,734}

Taking a clinical history directed to the potential cause of the disease is critical. Clinical and laboratory investigation and requesting tests should provide for the proper assessment of BP and the presence of acute EOD. Initially, BP should be measured in both arms, preferably in a calm environment, and repeatedly until stabilization (minimum of three measurements). Data on the patient's typical BP should be rapidly collected, as well as information on situations that can trigger BP increases and comorbidities; the use or discontinuation of antihypertensive medications (particularly adrenergic antagonists); or the use of substances that can increase BP (see Chapter 15). A systematic approach, including an assessment of signs and symptoms, physical examination and complementary investigation, helps determine the presence of acute and progressive EOD, as shown in Chart 13.3:

13.5. General Treatment of Hypertensive Crisis

Treatment of HU (Figure 13.1) should begin after a period of clinical observation in a calm environment, which helps rule out cases of pseudocrisis (treated only with rest or the use of painkillers or tranquilizers). Captopril and clonidine are indicated for acute treatment. Captopril, at a dose of 25-50mg, has peak action within 60 to 90 minutes, while clonidine is fast-acting, working in approximately 30 to 60 minutes, at a dose of 0.100 to 0.200mg. The use of immediate-release nifedipine capsules to treat HU should be banned, because it is neither safe nor effective, and causes rapid and marked BP reductions, which can result in tissue ischemia.^{745,746}

There is no evidence from randomized controlled trials showing antihypertensives reduce morbidity and mortality for individuals with HE. However, based on clinical experience and the progress of patients under treatment, antihypertensive treatment is beneficial and cuts mortality. The treatment of patients with HE is aimed at rapid BP reduction to prevent the progression of EOD. Individuals should be preferentially admitted to the ICU, treated with intravenous (IV) antihypertensives, and carefully monitored during treatment to prevent hypotension. The general recommendations for BP reduction for HE are (LR: I; LE: C):^{5,164}

- Mean BP $\leq$ 25% in the 1st hour;
- BP 160/100-110 mm Hg in 2 to 6 h;
- BP 135/85 mm Hg in 24-48 hours.

However, HEs should be approached considering the impaired system or end-organ.

13.6. Hypertensive Emergencies in Special Situations

Chart 13.4 shows the medications indicated for the main forms of HE.

13.6.1. Hypertensive Encephalopathy^{747,748}

Hypertensive encephalopathy is a neurological HE characterized by signs and/or symptoms of cerebral edema secondary to sudden and/or sustained BP elevation. In

general, it is found in chronic hypertensive patients who develop accelerated/malignant hypertension or in previously normotensive individuals with sudden increases in BP progressing to the failure of cerebral perfusion autoregulation mechanisms. It is also characterized by insidious onset and progresses with headaches, nausea, or vomiting. There may be changes to the visual field, photopsia, blurred vision, visual hallucinations, confusion, coma, generalized convulsive crises, and hyperreflexia. Treatment consists of slowly lowering BP, since rapid and intense decreases may cause cerebral hypoperfusion and loss of cerebral autoregulation mechanism. Sodium nitroprusside (SNP) is recommended in Brazil. In other countries, the following medications are available: nicardipine, clevidipine, labetalol, and fenoldopam. In the first 24 to 48 h, oral antihypertensives should be administered to better control BP.

13.7. Stroke

Hypertension is the primary risk factor for strokes, especially hemorrhagic strokes.⁷⁴⁹ Diagnosis is based on a full neurological examination; for severity assessment purposes, use the National Institute of Health Stroke Scale (NIHSS). Head CTs and MNRs enable physicians to define the type of stroke (ischemic stroke in 85% of cases, hemorrhagic stroke in 15% of cases) and the area involved.^{164,750} For incipient infarctions, an MNR is more sensitive than a CT.

13.7.1. Ischemic Stroke

BP often decreases spontaneously within 90 to 120 minutes during the acute phase. The recommendations are as follows:

1. In case of ischemic stroke with indication for thrombolysis, BP reduction $<$ 185/110 mm Hg before fibrinolytic therapy is recommended (LR: I; LE: B).^{5,652} If BP remains $>$ 185/110 mm Hg, thrombolytic therapy should not be administered. That recommendation also applies to individuals who are to undergo thrombectomy.⁷⁵¹ BP should be maintained $<$ 180/105 mm Hg in the first 24 hours after thrombolysis.
2. An initial 15% decrease in BP can be applied in cases of very high BP ($\geq$ 220/120 mm Hg) and other associated HEs (aortic dissection, acute coronary events, eclampsia, post-thrombolysis, and/or APE) (LR: I; LE: C).^{5,652}
3. In patients with BP $\geq$ 220/120 mm Hg that have not received thrombolytics and do not present with other HE requiring antihypertensive treatment, the benefit of starting or restarting treatment for hypertension in the first 48 to 72 h is unclear. It seems prudent to reduce BP by 15% during the first 24 h after the beginning of the ischemic stroke (LR: IIb; LE: C).^{5,652}
4. Starting or restarting antihypertensive therapy during hospitalization for neurologically stable patients with BP $\geq$ 140/90 mm Hg is safe for improving long-term BP control (LE: B; LR: IIa).^{5,652}
5. In other cases of ischemic stroke, reducing BP within 5 to 7 days of the event has controversial neurological effects requiring treatments be tailored for individual patients (LR: I; LE: A).⁶⁵²

13.7.2. Hemorrhagic Stroke

Elevated BP increases the risk of hematoma expansion and death, in addition to worsening the prognosis for neurological recovery. However, there is no conclusive evidence in favor of rapid reductions of BP. Cerebral edema occurs in 30% of cases, usually during the first 24 hours. In those cases, decompressive craniectomy should be performed and patients transferred to specialized centers (LR: I; LE: B).^{5,752}

For individuals with acute presentation (< 6 h from onset of hemorrhagic stroke):

1. SBP > 220 mm Hg – consider BP reduction with continuous IV infusion and frequent BP monitoring (LR: IIa; LE: C).^{5,752}
2. SBP from 150 to 220 mm Hg – lowering BP below 140 mm Hg provides no benefits in terms of lower mortality or severe impairment and is potentially dangerous (LR: III; LE: A).^{5,752} Consider a target SBP < 180 mm Hg.³⁷

13.7.3. Acute Coronary Syndromes

Coronary syndromes can be accompanied by BP elevation due to a reflex triggered by the ischemic myocardium. Consequently, higher PVR increases myocardial oxygen demand. The goal is to reduce the afterload without increasing the heart rate or reducing preload too much, since it would lead to increased myocardial oxygen consumption. The goal should be SBP < 140 mm Hg (avoid < 120 mm Hg) and DBP between 70 and 80 mm Hg using esmolol, metoprolol, or nitroglycerin (LR: I; LE: A). Intravenous nitrates reduce PVR, improve coronary perfusion, and have an important systemic vasodilator effect, reducing preload and myocardial oxygen consumption. Hydralazine, SNP, and nifedipine use is contraindicated, since it may promote flow steal.^{164,733} The recommendations are:

- a) Intravenous nitroglycerin (NTG) is indicated in the first 48 hours for treatment of hypertension, persistent ischemia³ and HF, as long as hypotension, right ventricular infarction, or use of phosphodiesterase type 5 inhibitors have not been present in the previous 48 h (LR: I; LE: B). NTG use should not exclude other interventions that have proven to reduce mortality, such as beta-blockers (BBs) or ACEIs.^{753,754}
- b) The use of IV BBs is indicated for hypertensive individuals who do not present with: 1) signs of HF; 2) clinical evidence of low CO; 3) increased risk for cardiogenic shock; or 4) other contraindications for beta blockade (LR: IIa, LE: B).^{753,756}

13.7.4. Acute Pulmonary Edema (APE)

Approximately one third of the patients admitted with APE and HE have preserved left ventricular function, and myocardial ischemia may also be involved in the pathophysiology of APE associated with HE.^{755,756} HE with APE should be controlled primarily in an ICU setting, with IV medication, monitoring, and gradual BP reduction. NTG and SNP are used to lower preload and afterload. Loop diuretic use also lower volume overload and, consequently, BP. In some cases, the use of noninvasive continuous positive airway pressure may be indicated for decreasing pulmonary edema and venous return.^{747,748,757}

13.7.4.1. Acute Aortic Dissection

In patients with precordial pain and high BP, acute aortic dissection should always be considered. The progression of dissection is related to BP level and ventricular ejection velocity.⁷⁵⁸ Achieving proper pain management (IV opiates for analgesia), HR < 60 bpm, and SBP between 100 and 120 mm Hg are important (LR: I; LE: B).^{5,747,758} SBP < 120 mm Hg should be achieved in 20 minutes. The use of SNP in isolation is not ideal, since it increases HR and aortic ejection velocity, potentially worsening the dissection.^{5,747,758} Thus, SNP should be associated with a BBs, initially IV, short, and titrable (metoprolol, labetalol, or esmolol), to decrease the heart rate. Alternately for asthma patients, nondihydropyridine calcium channel blockers (CCBs) may be used.

13.7.5. Pre-eclampsia/Eclampsia (see Chapter 11)

13.7.6. HE from Illicit Drug Use

Illicit substances that increase BP are sympathomimetics, potentiating the effect of catecholamines, including amphetamines and ecstasy, their illegal derivative, in addition to powder cocaine and smokable crack cocaine.^{5,759,760} Amphetamine use causes a dose-dependent increase in BP,⁷⁶¹ leading to tachycardia, palpitations, sweating, and arrhythmias, while ecstasy has other effects in addition to HR and BP increases (serotonergic syndrome).⁷⁶²

Intranasal cocaine use leads to a sudden and dangerous increases in BP levels within 15 minutes of use. In case of preexisting hypertension, higher BP elevations may occur.⁷⁶³ Cocaine-induced vasoconstriction depends on the central sympathetic discharge, which is suppressed by the intact baroreceptor function. When the baroreflex tamponade is impaired, the result is adrenergic vasoconstriction and HC.⁷⁶⁴

In lighter cases, benzodiazepines and sublingual NTG may be administered. In more severe cases, IV therapy will probably be required, the agents of choice are NTG, SNP, or phentolamine.^{759,760} It is important to avoid BBs, since they may lead to alpha-adrenergic receptor stimulation in the presence of beta blockade, thus causing a coronary spasm.⁷⁶³ An exception might be carvedilol, which is capable of mitigating HR and BP increases induced by smoking crack cocaine.⁷⁶⁵ CCBs may also be used in cases of cocaine-induced AMI, where the assumed cause is coronary vasoconstriction.⁷⁶⁰

A complicating factor of those intoxications, whether they are HUs or HEs, is the concomitant ingestion of high doses of caffeine (present in energy drinks), nicotine, or alcohol, which increase plasma NE levels.⁷⁶⁶ In particular, alcohol and cocaine use in combination has a greater toxic effect than the use of either alone,^{767,768} increasing the risk of sudden death 18- to 25-fold⁷⁶⁹ due to increased bioavailability of cocaine.⁷⁷⁰ Treatment includes the use of BBs, alpha-blockers, and CCBs, the latter administered before or after cocaine intake.^{760,771}

13.7.7. Accelerated/Malignant Hypertension

Malignant hypertension is characterized by the presence of severe general hypertension, retinopathy with papilledema, with or without renal and/or heart failure, fibrinoid necrosis

of renal arterioles, and endarteritis obliterans, and may present with rapidly progressive and fatal clinical evolution. Elevated BP in the presence of retinal hemorrhages and exudates in the funds, but in the absence of papilledema, is known as accelerated hypertension. Currently, the terms “malignant” and “accelerated” are considered interchangeable, with “accelerated/malignant hypertension” used more often to define this form of HE, which, though less frequent, represents a devastating form of acute BP elevation.^{747,772,773} The prognosis is almost always fatal if not properly recognized and left untreated, with two-year mortality rates of approximately 80%, primarily due to HF and CKD.^{774,775} Effective treatment of malignant hypertension has significantly improved survival, but it is still accompanied by a high rate of complications.⁷⁷⁶ The most rational way to manage is to prevent it by treating hypertension early and effectively. Individuals with severe hypertension who present with major LVH and renal failure should be treated as prior accelerated/malignant hypertension patients.

Patients should undergo intensive BP control using immediate-action vasodilator medications, such as SNP, which promotes fast BP control and makes individuals more responsive to classic antihypertensive therapeutics.^{164,732} During acute control, oral antihypertensives should be administered, including diuretics, renin-angiotensin system blockers, BBs, direct-acting vasodilators (hydralazine), central adrenergic agonists (clonidine and methyldopa), and CCBs, when multiple medications are required.^{747,774} BB use is indicated for cases of pulmonary congestion caused by diastolic dysfunction due to

severe LVH. BP reductions should be gradual, keeping DBP levels above 100 mm Hg during the first few days of treatment. There may be an initial impairment in kidney function with high creatinine levels since the mechanism of autoregulation of renal flow is shifted to much higher levels than those found in mild hypertensive patients and normotensive individuals. Therefore, an adjustment period is required before returns to baseline levels. Sometimes, dialysis treatment may be required during the most acute stage. Antihypertensive treatment for this condition has had a significant impact on survival (LR: IIa; LE: B).

13.7.8. Hypertension with Multi-Organ Damage

Hypertension with multi-organ damage (MOD) is defined by the concurrent involvement of three of the four systems listed below:⁷⁷⁷

- Renal (rapid decline of kidney function or proteinuria);
- Cardiac (major LVH or systolic dysfunction, or ventricular repolarization abnormalities, or increased troponin);
- Neurological (stroke or hypertensive encephalopathy);
- Hematological (microangiopathic hemolysis).

The definition of MOD hypertension (in the presence of multi-organ impairment) does not require the presence of Keith-Wagener Grade III or IV changes, which may be found at a later stage.^{778,779} When comparing MOD hypertension to accelerated/malignant hypertension, the two are found to have analogous pathogeny, clinical significance, and prognosis, implying similar clinical management (LR: IIa; LE: B).^{777,780}

Key Takeaways

Hypertensive crisis: acute elevation of systolic blood pressure (BP) ≥ 180 mm Hg and/or diastolic BP ≥ 120 mm Hg, which may or may not result in end-organ damage (EOD), divided into hypertensive urgencies (BP increase without EOD and no imminent risk of death, allowing for BP reduction within 24 to 48 h) and hypertensive emergencies (BP increase with acute EOD or in progress and immediate risk of death, requiring rapid and gradual BP decrease within minutes to hours using intravenous medication).

Hypertensive emergencies may manifest as a cardiovascular, cerebrovascular, renal or multi-organ event, or even as pre-eclampsia with severe features or eclampsia.

High BP without acute and progressive EOD rules out HE.

Uncontrolled hypertension from low adherence, difficult-to-control hypertensive pseudocrises, hypertensive urgencies, and hypertensive pseudocrises are common situations of high BP without acute or progressive EOD.

The severity of the clinical condition is not determined by absolute BP levels, but rather by the magnitude and timing of the increase. Numerical values act as a parameter, but should not be applied as absolute diagnostic criteria.

Chart 13.1 – Classification of hypertensive emergencies

HYPERTENSIVE EMERGENCIES
Cerebrovascular • Hypertensive encephalopathy • Ischemic stroke • Hemorrhagic stroke • Subarachnoid hemorrhage Cardiocirculatory • Acute aortic dissection • Acute pulmonary edema with left ventricular failure • Acute coronary syndromes Kidney/multiple organ failure • Accelerated/malignant hypertension • MOD hypertension
• Severe adrenergic crises • Pheochromocytoma crisis • Drug overdose (cocaine, crack cocaine, LSD)
• Gestational hypertension • Eclampsia • Pre-eclampsia with severe features • HELLP syndrome • Severe hypertension at the end of pregnancy

MOD: multi-organ damage. HELPP: hemolysis, elevated liver enzymes, low platelets. Adapted from Malachias et al., 2016;¹⁶⁴ Bortolotto et al., 2018;⁷³³ Martion & Ribeiro, 2015;⁷³⁴ Whelton et al., 2018;⁵ Cremesp, 2004;⁷⁴⁶ Williams et al., 2018;³⁷ Ma et al., 2020.⁷⁷⁸

Chart 13.2 – Diagnosis, prognosis, and management of hypertensive urgencies and emergencies

Urgency	Emergency
Markedly high BP level	Markedly high BP level
Without acute and progressive EOD	With acute and progressive EOD
Oral drug combination	Parenteral medication
No imminent risk of death	Imminent risk of death
Early outpatient follow-up care (7 days)	Preferential ICU admission

EOD: end-organ damage; ICU: intensive care unit.

Chart 13.3 – Clinical and complementary investigation by end-organ damage of hypertensive emergencies

Primary damage in HE	Symptoms	Physical examination	Complementary investigation at physician's discretion
Cardiovascular	- Chest, abdominal, or back pain or discomfort; - Dyspnea; fatigue; coughing.	- HR, heart rhythm, pulse changes, gallop rhythm, jugular venous distension, and pulmonary, abdominal, and peripheral congestion; - Heart and vascular murmurs; - Four-limb blood pressure palpation.	- ECG, O₂ saturation, chest X-ray, myocardial necrosis markers, BNP, lactate dehydrogenase; - Echocardiogram; - Angiotomography, chest CT, and chest MNR.
Neurological	- Dizziness; headaches; - Impaired sight, hearing or speech;	- Consciousness or coma level; agitation, delirium or confusion; seizures; focal deficits; neck stiffness.	- Head CT; head MNR
Renal	- Change in urination frequency and volume;	- Edema or dehydration; - Change in urine aspect (hematuria); - Abdominal masses and murmurs.	- Urine I; creatinine; urea; Na⁺; K⁺; chlorine; blood gas analysis.
Fundus		- Papilledema; hemorrhages; exudates; - Vascular changes, such as spasms, pathological arteriovenous crossings, arterial wall thickening, and silver- or copper-wire aspect.	
Minimum additional tests	- ECG, chest X-ray, myocardial necrosis markers, CBC with platelet count, creatinine, urine I, and potassium.		

BNP: atrial natriuretic peptide; CT: computed tomography; ECG: electrocardiogram; HE: hypertensive emergency; HR: heart rate; MNR: magnetic nuclear resonance. Adapted from Malachias et al., 2016;¹⁶⁴ Bortolotto et al., 2018;⁷³³ Martion & Ribeiro, 2015;⁷³⁴ Whelton et al., 2018;⁵ Vilela-Martin et al., 2020.⁷⁴⁷

Guidelines

Chart 13.4 – Parenteral medications used to treat hypertensive emergencies

Drugs	Route of administration and dosage	Beginning	Duration	Indications	Adverse events and precautions
Sodium nitroprusside (arterial and venous vasodilator, stimulates cGMP formation)	Continuous infusion 0.25-10 mg/kg/min IV	Immediate	1-2 min	Most hypertensive emergencies	Cyanide poisoning, severe hypotension, nausea, vomiting. Attention in kidney and liver failure and high intracranial pressure. Protect from light.
Nitroglycerin (arterial and venous vasodilator)	Continuous IV infusion 5-15mg/h	2-5 min	3-5 min	Coronary failure, left ventricular failure with APE	Headache, reflex tachycardia, tachyphylaxis, flushing, methemoglobinemia
Metoprolol (selective beta-adrenergic blocker)	5 mg IV (repeat every 10 min, if necessary up to 20 mg)	5-10 min	3-4 h	Coronary failure Acute aortic dissection (in combination with SNP)	Bradycardia, advanced AVB, heart failure, bronchospasm
Esmolol (ultra-rapid selective beta-adrenergic blocker)	Attack: 500µg/kg Intermittent IV infusion 25-50 µg/kg/min ↑ 25 µg/kg/min every 10-20 min. Maximum 300 µg/kg/min	1-2 min	1-20 min	Acute aortic dissection (in combination with SNP) Severe postoperative hypertension	Nausea, vomiting, 1st-degree atrioventricular block, bronchospasm, hypotension
* Phentolamine (alpha-adrenergic blocker)	Continuous IV infusion: 1-5mg. Maximum 15mg	1-2 min	3-5 min	Excess of catecholamines	Reflex tachycardia, flushing, dizziness, nausea, vomiting
* Trimethaphan (SNS and PSNS ganglionic blocker)	Continuous IV infusion: 0.5-1.0 mg/min. ↑ 0.5mg/min up to maximum of 15mg/min	1-5 min	10 min	Excess of catecholamines Acute aortic dissection	Tachyphylaxis
Hydralazine (direct-acting vasodilator)	10-20 mg IV or 10-40 mg IM every 6 h	10-30 min	3-12 h	Eclampsia	Tachycardia, headache, vomiting. Worsening of angina and infarction. Attention to high intracranial pressure
Diazoxide (vasodilator of arteriolar smooth muscle)	IV infusion 10-15 min 1-3 mg/kg Maximum 150 mg	1-10 min	3-18 h	Hypertensive encephalopathy	Retention of sodium, water, hyperglycemia, and hyperuricemia
* Fenoldopam (selective dopaminergic agonist)	Continuous IV infusion 0.1-1.6 µg/kg/min	5-10 min	10-15 min	Acute renal failure	Headache, nausea, flushing
* Nicardipine (calcium channel blocker)	Continuous IV infusion 5-15mg/h	5-10 min	1-4 h	Stroke Hypertensive encephalopathy Left ventricular failure with APE	Reflex tachycardia, phlebitis, avoid in patients with heart failure or myocardial ischemia
* Labetalol (alpha- and beta-adrenergic blocker)	Attack: 20-80 mg IV every 10 min Continuous IV infusion 2mg/min (maximum 300 mg/24 h)	5-10 min.	2-6 h	Stroke Acute aortic dissection (in combination with SNP)	Nausea, vomiting, atrioventricular block, bronchospasm, orthostatic hypotension
* Enalapril (ACE inhibitor)	Intermittent IV infusion 5.0 mg every 6 h up to 20 mg	15 min.	4-6 h	Left ventricular failure with APE	Hypotension, kidney failure, gestation
Furosemide (loop diuretic)	20-60 mg IV (repeat after 30 min)	2-5 min	30-90 min.	Left ventricular failure with APE Hypervolemic conditions, such as CKD, ADGN	Hypopotassemia

* Not available in Brazil. ACEI = angiotensin-converting enzyme inhibitors; ADGN = acute diffuse glomerulonephritis; APE = acute pulmonary edema; AVB = atrioventricular block; CKD = chronic kidney disease; IV = intravenous; PNS = parasympathetic nervous system; SNP = sodium nitroprusside; SNS = sympathetic nervous system. Adapted from Malachias et al., 2016;¹⁶⁴ Bortolotto et al., 2018;⁷³³ Martion & Ribeiro, 2015;⁷³⁴ Whelton et al., 2018;⁵ Vilela-Martin et al., 2020.⁷⁴⁷

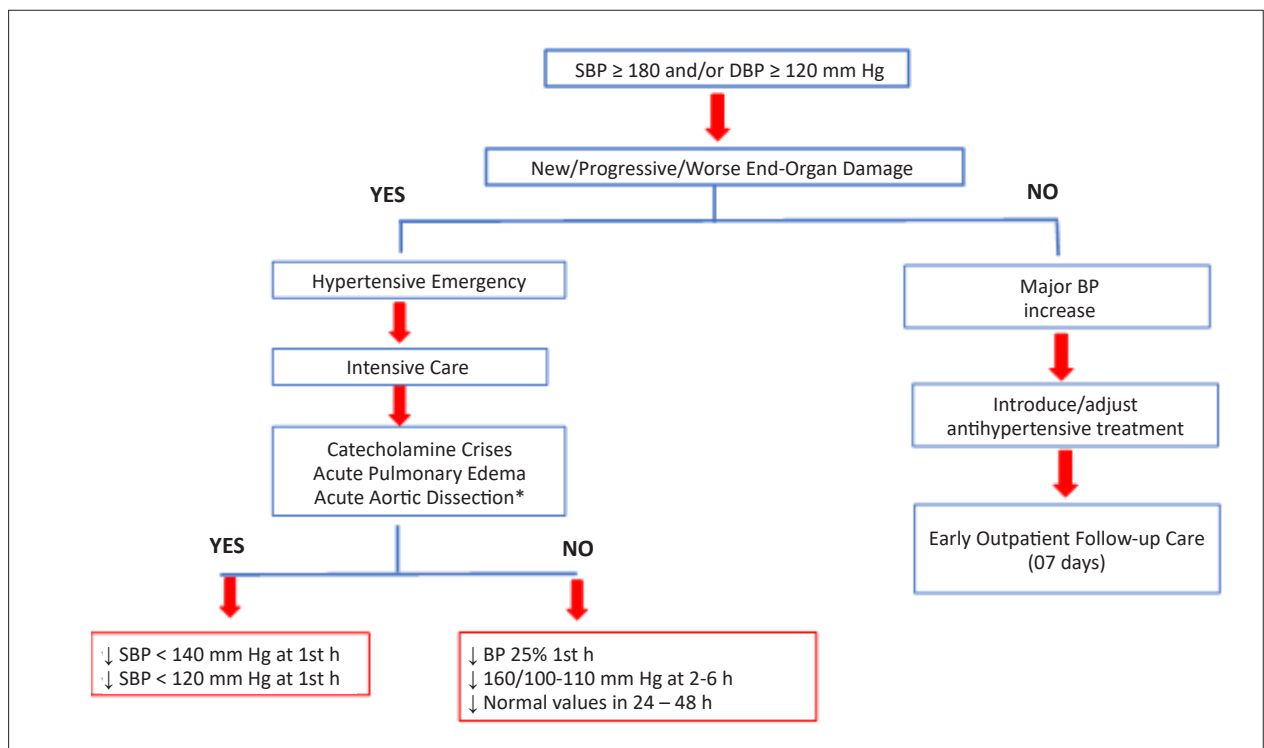


Figure 13.1. – Patient care flow chart for hypertensive crisis.
Adapted from Whelton et al., 2018.⁵

14. Hypertension in Older Adults

14.1. Introduction

The United Nations (UN) and the World Health Organization (WHO) consider as older adults all individuals age 60 and older. In high-income countries, where life expectancies are greater, the threshold has been raised to 65.⁷⁸¹ A special age group known as the “oldest old,” consisting of individuals ages 80 or older, represents the fastest-growing segment of the population.⁷⁸²

The prevalence of multimorbidity increases with age, and over two thirds of the oldest old suffer from two or more chronic illnesses.^{783,784} Based on a country-level study of the older adult population (ELSI-BRASIL), over 60% of older adults suffered from multiple chronic illnesses, and hypertension (HT) was the second most prevalent, second only to chronic back pain.⁷⁸⁵ These patients usually take multiple medications with hard-to-manage therapy regimens that increase their cost and the risk of drug interactions.

There is a direct and linear relationship between blood pressure (BP) and age, with the prevalence of HT going from approximately 7% in individuals ages 18 to 39 to over 60% in those 65 and older. The Framingham has shown that nearly two thirds of men and three fourths of women have HT at age 70.^{786,787}

Though epidemiological studies have suggested greater survival rates for individuals age 80 and older with high levels of BP, this may in part be caused by the fact that people with low BP have higher rates of multimorbidity and frailty, and therefore

lower probability of survival. In the geriatric population, HT is the primary modifiable risk factor (RF) for cardiovascular morbidity and mortality,⁷⁸⁶ even at more advanced ages. It is critical that we stress that HT is a modifiable RF for cognitive decline, dementia and disability.^{787,788}

In assessing mean survival rates for older adults, one should not use life expectancy at birth, but rather life expectancy “at life.” Therefore, life expectancy at age 80, in 2018, was 10.4 years for women and 8.6 years for men, more than enough time to enjoy the benefits of treatment for HT.

14.2. Physiopathological Mechanisms

Diastolic blood pressure (DBP) increases until approximately age 50, stabilizes from 50 to 60 and then decreases, while systolic blood pressure (SBP) tends to increase throughout the lifespan. Therefore, pulse pressure (PP = SBP – DBP), a useful hemodynamic index of arterial stiffness, increases with age. These changes are consistent with the idea that, for younger individuals, BP is largely determined by peripheral vascular resistance (PVR), while for older adults it is determined by central arterial stiffness.⁷⁸⁹⁻⁷⁹¹

The arterial wall thickening and endothelial dysfunction observed during the aging process are accompanied by increased stiffness and lower vascular compliance, attributed to a wide range of factors, such as salt sensitivity, chronic hemodynamic stress, and elastin fiber fragmentation and misalignment, with replacement by collagen fibers, facilitating the deposition of calcium ions.⁷⁹²

Aortic stiffening caused by vascular aging accelerates pulse wave velocity (PWV) towards peripheral circulation (centrifugal) and reflected waves returning to the heart (centripetal). The overlap of those two waves during the proto-mesostolic phase leads to the increases in SBP and wider PP seen in older adults.⁷⁹³

Currently, carotid-femoral PWV measurement is considered the gold standard to assess central arterial stiffness. In the absence of comorbidities, older adults with velocities under 7.6 m/s are considered to have good vascular health and, in an isolated sample, represent fewer than 4% of individuals age 60 and older.^{794,795} In a given urban region of Brazil, PWV values found in older adults, adjusted for BP, age and gender, averaged 9.1 m/s for normotensive individuals and 9.4 m/s for uncontrolled hypertensives.⁷⁹⁶ On the other hand, for many older adults, PP amplification may be a better predictor of events and mortality than PWV.⁷⁹⁷

14.3. Diagnosis and Therapeutic Decision

The presence of multiple comorbidities and polypharmacy may make investigating HT in older adults more difficult. Chapter 3 guidelines on BP measurement and physical and laboratory examinations should also be followed for this age group. However, the investigation of secondary causes of HT should proceed carefully and consider the risks and benefits for each procedure (see Chapter 15).⁷⁹⁸

The clinical assessment of older patients, especially the oldest old, is different from traditional assessments. First, physicians should recognize that the appointment will require more time due to several factors, such as: complexity of multiple associated conditions, physical and cognitive slowness of patient, and presence of caretakers and family members, with whom the physician will have to discuss the issues inherent to the relevant therapeutics and clinical conditions.⁷⁹⁹ Very frail older adults may require additional visits due to patient exhaustion.⁸⁰⁰

BP measurements may produce inaccurate values due to greater blood pressure variability and a few idiosyncrasies. Major factors interfering with BP measurement in older adults are: 1. auscultatory gap; 2. pseudohypertension; and 3. postural and postprandial variations.⁸⁰¹ (see Chapter 3)

Out-of-office BP monitoring, either ambulatory (ABPM) or at home (HBPM), is increasingly valued and indicated as a diagnostic tool for SHT in older adults.^{180,186} Despite its limitations, self-measured BP should also be considered (see Chapter 3).

Proper blood pressure treatment and control for hypertensive older adults and the oldest old has unequivocal benefits, such as significant decreases in stroke, AMI, HF, and mortality,^{87,509,572,802,803} in addition to preventing cognitive decline and possibly dementia.^{103,804-806} On the other hand, exact BP levels for treating older patients, as well as treatment targets, have been the subject of debate,¹⁸⁰ and different guidelines provide different recommendations.^{5,37,807} However, all guidelines, including this one, consider it key to perform individualized assessments. In addition to chronological age, we recommend weighing functional fitness, cognition, degree of frailty, patient expectations, comorbidities, end-organ

damage and global CV risk, polypharmacy, and treatment tolerability. Recommended blood-pressure levels for older adults, both for initiating treatment and blood-pressure targets, can be found in Chart 14.1.

14.4. Treatment

There is no single therapeutic strategy for older adults, especially those over the age of 80 to 85 (Chart 14.2). Therefore, other factors should be considered above age itself while planning the treatment: presence of comorbidities, autonomy, functional status, and degree of frailty (LR: I; LE: C). That stratification is a better predictor of possible complications both in the short and the long term in relation to different comorbidities.^{808,809} No therapeutic intervention should be denied or withdrawn based on age alone (LR: I; LE: C).

14.4.1. Nonpharmacological Treatment

All lifestyle change (LSC) measures that apply to younger individuals (see Chapter 8) are valid for older adults as well (LR: I; LE: B), but require greater care and more thoughtful consideration of their actual benefits—and potential risks. Older adults are more salt-sensitive, and dietary salt restrictions are more effective for this age group.⁴²⁰ The TONE study showed that there was a 4.3 mm Hg decrease in SBP and a 2.0 mm Hg decrease in DBP for every 80 mmol of sodium (= 2.0 g of salt) reduction in daily salt intake. Combined with concurrent weight loss, the BP reduction effect was potentiated.⁸¹⁰ Excess reduction in salt intake may lead to hyponatremia and loss of appetite and can cause malnutrition. Potassium-rich diets should be encouraged,⁸¹¹ but require greater attention to the risk of hypercalcemia due to the frequent presence of chronic kidney disease (CKD) and the use of medications that lower potassium excretion.

Physical exercise and aerobic and resistance training are critical for older adults and should be recommended.⁵² In older adults, especially the frail and sarcopenic, weight loss without physical exercise and adequate protein intake may lead to loss of muscle mass and worse functional fitness.

Smoking and alcohol abuse are still prevalent in older populations and should be discussed. Likewise, all medications in use by the patient need to be analyzed, as some may cause BP increases.

In recommending LSCs, physicians should consider the patient's degree of frailty, functional fitness, and other social and clinical aspects. Follow-up by a multidisciplinary team (see Chapter 7) and family/caretaker engagement are even more important for older patients.

14.4.2. Pharmacological Treatment

In choosing antihypertensive medication(s) for older adults, physicians should consider the high rates of comorbidities, specific contraindications, likely drug interactions and cost, as well as the availability of and clinical experience with the medication (LR: I; LE: C). Prudence dictates initiating monotherapy or combination therapy at low doses and, if needed, increase or gradually combine antihypertensives at intervals of at least two weeks (LR: I; LE: C).

Chapter 9 details when to give preference or to avoid specific antihypertensives and their combinations. Here, we highlight aspects peculiar to older patients.

The first antihypertensive may be a thiazide (or thiazide-like) diuretic, a calcium channel blocker (CCB), or a renin-angiotensin-aldosterone system (RAAS) blocker: an angiotensin-converting enzyme inhibitor (ACEI), or an angiotensin II AT₁ receptor blocker (ARB). A large number of clinical trials have studied these four classes, and they are widely used in guidelines for older adults.⁸⁰⁷⁻⁸⁰⁹ In terms of monitoring, indications and care are similar to those for other adults (see Chapter 9).

Beta-blockers (BBs) should not be used as initial monotherapy for older adults,⁸⁰⁹ except in the presence of certain comorbidities, which may actually make their indication mandatory, such as heart failure (HF) or acute coronary failure (LR: I; LE: A).^{812,813} Patients suffering from bronchial asthma or chronic obstructive pulmonary disease (COPD), but with clinical indication for BBs, should be carefully treated with cardioselective BBs and after receiving respiratory compensation, and should not be deprived of their benefits.⁸¹⁴ When used in combination with acetylcholinesterase inhibitors, frequently used for Alzheimer's disease, they may induce severe bradycardia.⁸¹⁵

Other classes of antihypertensives (centrally acting medications, aldosterone antagonists and direct vasodilators), as well as other invasive treatments of the sympathetic nervous system, should be seen as the exception and not used as a matter of course to treat older patients (LR: III; LE: C) (see Chapter 9).

The risk of falls in older adults can increase during the first weeks of treatment with DIUs, and with all other medication classes in the first day. In the long run, antihypertensives may actually have protective effects.^{816,817}

14.5. Special Situations

There is some disagreement between results from observational studies and those from randomized clinical trials (RCTs). They come primarily from the fact that frail, multimorbid older adults are underrepresented in RCTs and the high risk of bias in nonrandomized and observational studies, where the longer survival of patients with high BP may be explained by their greater organ reserve.⁸¹⁸⁻⁸²²

14.5.1. Functional Status and Frailty: Assessment and Implications

In older adults, and especially in the oldest old, functional status and frailty require special attention. With the use of systematic tests and scales, the comprehensive geriatric assessment (CGA) enables an accurate global assessment of older adults and the development of therapeutic strategies.^{823,824} Though the ideal form of assessment, it may require the presence of a geriatrician or gerontologist. In day-to-day care for older hypertensive patients, clinicians should assess functional status and capacity to perform the activities of daily living.^{825,826}

Routine use of the gait speed test (GST) is recommended, as it is easily performed as part of regular visits and has been

shown to be a prognostic predictor of survival.^{827,828} Patients are considered frail or at risk of frailty when GST < 0.8 m/s (unable to walk 6 m in less than 8 seconds), requiring further investigation.^{820,829} In addition, this guideline recommends the use of the “Escala Clínica de Fragilidade,” which has already been translated into Brazilian Portuguese and validated in Brazil,⁸³⁰ based on the Canadian *Clinical Frailty Scale*, widely tested and deployed, as it is simple and reliable, provides a global view of patient condition, and determines the prognosis.^{827,828,831,832}

Frailty is associated with higher risk of HT, subclinical disease, CV events, and death.^{821,833-835} Adequate HT control may influence the trajectory of frailty. On the other hand, advanced levels of frailty are associated with lower BP values, lower body mass index (BMI), less muscle mass, impaired cognition, and higher mortality.^{335,836}

Functionally active and independent patients with no severe comorbidities have enough organ reserve and mean survival to enjoy most of the benefits from antihypertensive treatment and should, if well tolerated, have the same blood-pressure targets as younger older adults (LR: I; LE: B).^{335,805,825,831} On the other end of the scale, individuals with major functional loss, sarcopenia, frailty, or advanced dementia, or unable to perform self-care activities, should have their whole treatment regimen and blood-pressure targets reassessed.^{821,825,831,837} The primary goal is to improve symptoms and quality of life. Frailer older adults were systematically excluded from several clinical trials, so studies focused specifically on this population are key.^{307,821}

Between the two extremes we find older adults with intermediate functional status and multiple non-CV comorbidities who may require very challenging therapeutic decisions. For them, deeper assessments may be critical to define the real risk-benefit ratio and to individualize therapeutic strategies.^{307,825,831,838,839}

14.5.2. Cognitive Decline and Dementia

In addition to its well-known role as the primary cause of strokes, HT has also been implicated as a pathogenic factor in cognitive impairment, both vascular and from Alzheimer's disease, the main causes of dementia in older adults, and more markedly in the long run.⁸⁴⁰⁻⁸⁴²

In several epidemiological studies, use of antihypertensive medications is associated with less cognitive decline and dementia, especially in the long run.⁸⁴³ RCTs have found decreased white matter damage and cognitive decline from treatment for HT, with intensive treatment even more efficient in that regard.^{5,37,844} RCTs have not yet clearly proven decreased dementia. This may be because cognition was not the primary outcome in those RCTs, the lack of uniformity in the definition of dementia and in what tests were used, or the short duration of the trials.^{806,845}

14.5.3. Polypharmacy and Adherence

Polypharmacy, defined as the regular use of five or more medications, is increasingly frequent with age,⁸⁴⁶ and is associated with higher probability of adverse events (AE), drug interactions, and worse adherence to treatment.⁸⁴⁵

Improper adherence to pharmacological treatment is a frequent issue for older adults and one of the primary causes of inadequate BP control. Determinants of poor adherence to therapeutic regimens include misunderstanding the disease, polypharmacy, multiple daily doses, and side effects.⁸⁴⁷ To that end, this guideline recommends, especially for older adults with polypharmacy, the periodic review of each prescribed medication, AE assessments,⁸⁴⁸ and that antihypertensive treatment include as few pills and tablets per day as possible, using single-tablet fixed-dose combinations, in addition to emphasizing nonpharmacological measures (LR: I; LE: A) (see Chapter 17).

14.5.4. Deintensification and Deprescription

In different clinical situations, it may be necessary to gradually lower dosage or even deprescribe antihypertensive medications; these include symptomatic hypotension; adverse reactions; persistently below-target SBP detected out-of-office or at the physician's office;⁸²²⁻⁸²⁴ changing blood-pressure targets to less rigid levels (keeping in mind that BP tends to decrease at very advanced ages due to progressively lower organ reserve and greater frailty); and end-of-life palliative care.⁸³⁷

A key issue in treating HT in older adults, especially in the oldest old, is the careful monitoring of AEs and tolerability, with special attention to atypical signs and symptoms. Discontinuing antihypertensives seems to be safe in the short run, but without

proven benefits for cognition or functional fitness to perform the activities of daily living (ADLs).^{838,849,850}

14.5.5. Orthostatic and Postprandial Hypotension

Because of arterial stiffness, variations in volume significantly interfere with HT control. Older adults have weaker baroreceptor reflex to hypotension, and so are likely to be subject to orthostatic hypotension (OH) and postprandial hypotension (PPH). A higher rate of neurodegenerative disease is also associated with this condition.⁸⁵¹ Approximately 20% of older adults have OH and around 30% of institutionalized older adults experience hypotension after meals.^{852,853} Therefore, older adults should be carefully monitored for OH and PPH (LR: I; LE: B).

In RCT, HT control led to fewer CV events with no increased risk of OH or falls with injuries.⁸⁵⁴⁻⁸⁵⁶ Poorly controlled HT and certain antihypertensive medications, such as alpha-blockers, can cause or worsen OH. The best option to control OH is to use nonpharmacological interventions, such as adequate hydration, adequate sodium intake, slow rise from decubitus, higher headrests, and compression socks.⁸⁵³

In postprandial hypotension, older adults should avoid large meals and high intake of alcohol and carbohydrates. They should also avoid exercising after meals. In addition, medication prescriptions should be revised in order to lower polypharmacy as much as possible, paying special attention to drugs that may be contributing to OH or PPH, such as DIU, sympatholytics, nitrates, and tricyclic antidepressants.

Key Takeaways

HT prevalence increases progressively with age, as do other RFs, leading to sharp rises in CV risk among older adults.

Proper diagnosis requires caution with the peculiarities of blood pressure measurement, and out-of-office BP readings (SMBP, HBPM, ABPM) are key in older adults, for whom inadequate treatment poses more risk.

Functional and cognitive status should be evaluated. Therapeutic decisions and BP targets should be based on functional status and survival over chronological age.

Treatment lowers CV risk as well as the risk of cognitive decline. Comorbidities, more frequent in older adults, should guide what medications are chosen or avoided.

Special attention should be given to family support networks, polypharmacy, adherence, and higher risk of OH.

Chart 14.1 – Hypertension treatment recommendations for older adults

Global condition ¹	Office SBP		Office DBP	
	Treatment threshold	Blood-pressure target ^{4,5}	Treatment threshold	Target ⁸
Healthy ²	≥140 (I, A)	130-139 (I, A) ⁶	≥90	70-79
Frail older adults ³	≥160 (I, C)	140-149 (I, C) ⁷	≥90	70-79

1: functional status is more important than chronological age; 2: including light frailty; 3: moderate to severe frailty; 4: including older adults with comorbidities: DM, CAD, CKD, stroke/TIA (not acute stage); 5: actively assess tolerability, including possible atypical symptoms; 6: stricter target (125-135 mm Hg) may be achieved in selected cases, especially for motivated older adults, < 80 years old, with optimum treatment tolerability; 7: higher limits in case of limited survival and absence of symptoms. BP reductions should be gradual; 8: DBP = avoid < 65-70 mm Hg in clinically manifested CAD patients. Note: out-of-office BP monitoring (ABPM/HBPM) should follow changes to the therapy regimen or be performed annually due to greater variability in BP with age, higher risk of orthostatic hypotension, and lower tolerability to inadequate treatment of white coat and masked hypertension.

Chart 14.2 – Challenges in treating SHT in older adults.**Most older adults are hypertensive, with high prevalence of ISH.**

The challenges are not limited to age, but primarily to functional, social, nutritional, and mental status.

Survival rate is more closely tied to global functional status than to age itself.

A diagnosis of HT in older adults requires acknowledging their idiosyncrasies and the frequent use of out-of-office monitoring.

Therapeutic challenges are connected to adherence, presence or absence of polypharmacy, orthostatic hypotension, and comorbidities, such as urinary incontinence and fatigue, among others, common in older adults.

Clinical assessments should include functional tests, such as gait speed and the Clinical Frailty Scale.

Treatment prevents CV events, death, and cognitive decline, even at advanced ages.

LSCs work, but require greater care.

DIUs, CCBs, ACEIs/ARBs should be used in isolation or combined as initial therapies; BBs, when there is formal indication for their use.

Weight loss and loss of organ reserve at advanced ages may be associated with gradual decreases in BP and may imply in treatment deintensification.

In older adults receiving palliative care for advanced disease or severe frailty, the primary treatment objective is symptom control.

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II AT1 receptor blocker; BB: beta-blocker; CCB: calcium channel blocker; CV: cardiovascular; DIU: diuretic; HT: hypertension; ISH: isolated systolic hypertension; LSC: lifestyle changes.

15. Secondary Hypertension**15.1. Introduction**

Secondary hypertension is the form of hypertension (HT) due to an identifiable cause and treatable by a specific intervention which can improve or resolve blood pressure control. The actual prevalence of secondary HT is unknown, but estimated at 10 to 20%,⁸⁵⁷ and may be higher or lower, depending on the population cohort (especially in terms of age), diagnostic resources available and physician expertise. It should be investigated when signs (clinical history, physical examination, or routine tests) lead to clinical suspicion²⁵⁸⁻⁸⁶⁰ (Chart 15.1).

The main causes of secondary hypertension, discussed in this chapter, are shown in Figure 15.1. Diagnostic investigation can focus on the age of the patient and the type of sign, as seen in Chart 15.2. Patients with secondary HT are under higher CV and renal risk and have more end-organ damage due to higher and more sustained BP levels, as well as the activation of hormonal and molecular mechanisms.^{859,861}

15.2. Nonendocrine Causes**15.2.1. Chronic Kidney Disease (CKD)**

CKD is defined by its cause and by functional or morphological abnormalities persisting for over three months with consequences for the patient's health. It is characterized by an estimated glomerular filtration rate (eGFR) < 60 mL/min or alterations in urine tests, especially albuminuria (30 mg/24 h or 30 mg/g albumin/creatinine ratio) and/or in renal morphology (LR: I; LE: C).⁸⁶² CKD classification and prognosis are based on eGFR and albuminuria levels (Chapter 4). HT is both cause and consequence of CKD and becomes progressively worse as kidney function declines, affecting 90% of stage 5 patients (LR: I; LE: A).^{863,864}

Tests for hypertensive patients should include serum creatinine and eGFR calculation (LR: I; LE: B) as well as urine

test (LR: I; LE: C) for CKD screening.⁸⁵⁹ Renal ultrasound, computed tomography (CT), or magnetic nuclear resonance (MNR) may also be necessary. Kidney biopsies are only required when there are rapid declines in eGFR, glomerular hematuria, and/or proteinuria/albuminuria in addition to HT.⁸⁶⁵ HT accelerates the progression of CKD, and lowering BP attenuates the course of CKD.^{863,864} Treatment goals and therapy regimens indicated for BP control in CKD patients can be found in Chapters 6 through 9.

15.2.2. Renovascular Hypertension (RVH)

Renovascular hypertension (RVH) is a common and potentially reversible cause of secondary HT due to partial or total, uni- or bilateral renal artery stenosis (RAS) or of one of its branches, triggered and maintained by significant renal ischemia. It is usually found in obstructions greater than 70%.¹⁶⁴ Its prevalence and etiology vary with age and blood pressure levels. In young adults, especially women, RVH is more frequently caused by fibromuscular dysplasia (FMD). In older adults, the most common cause is atherosclerosis, usually accompanied by peripheral and/or coronary atherosclerosis.⁸⁶⁶ The clinical indicators of RVH can be found in Chart 15.3.

In patients with potential signs of RVH, the physician should consider diagnostic tests for those with fewer morbidities for whom revascularization treatment is indicated.^{867,868} Renovascular disease has heterogeneous clinical manifestations. The damage may evolve with minimal or even silent hemodynamic repercussions before progressing to critical levels associated with triggering hypertensive physiopathological mechanisms and renal ischemia. Revascularization procedures are indicated for FMD patients and patients with atherosclerotic etiology who cannot control BP or are suffering progressive loss of renal function or decompensated heart failure (acute pulmonary edema, heart failure and refractory angina).⁸⁶⁹ A cost-effective investigation requires proper selection of candidates as well as anatomical and functional assessment of the stenosis.⁸⁶⁶

The gold standard is still conventional renal arteriography, but it is invasive and should not be used as the first procedure (LR: I; LE: B). BOLD or digital subtraction MNR angiography (LR: II; LE: B) and spiral CT are as accurate as ultrasounds, and have higher sensitivity and specificity (LR: I; LE: B). Renal Doppler US is the recommended noninvasive method for screening purposes, with 75% sensitivity and 90% specificity.^{267,869-871}

The treatment objectives for RVH are reducing the morbidity and mortality associated with high BP and protecting renal function and circulation. Randomized clinical trials⁸⁷² and a meta-analysis⁸⁷³ have shown^{874,875} that pharmacological treatment matches revascularization, with similar rates of BP control and cardiovascular mortality.

RAAS-blocking medication is recommended to lower hyperfiltration in the contralateral kidney and proteinuria in unilateral RVH with adequate potassium and creatinine monitoring. The efficacy of pharmacological optimization is an important element for decisions about whether an invasive procedure is indicated.⁸⁷⁴ Atherosclerotic RVH requires lifestyle changes, smoking cessation, glycemic control, and prescription of statins and antiplatelet drugs, unless contraindicated.^{874,876}

If the blood-pressure target cannot be reached and/or there are other associated clinical conditions, such as RHT or RfHT, progressive kidney dysfunction or APE episodes, the invasive procedure may be recommended, conditional on the patient's acceptance. The actual benefits of invasive treatment are controversial, and clinical trials are still needed to identify the specific population that would benefit from this sort of treatment.^{877,878} Diagnostic recommendations for renovascular disease can be found in Chart 15.4.

15.3. Fibromuscular Dysplasia

Fibromuscular dysplasia (FMD) is an idiopathic, segmental, stenotic, nonatherosclerotic, and noninflammatory disease of the small- and medium-caliber muscular arteries. The lesions may be symptomatic or clinically silent, hemodynamically significant or not. Approximately 80 to 90% of patients are females. The First International Consensus⁸⁷⁹ recommends angiographic classification for focal and multifocal FMD. For screening purposes, Doppler ultrasound of renal arteries is recommended. Other imaging examinations coincide with those used for atherosclerotic RVH: spiral CT if eGFR > 60 mL/min or MNR if eGFR > 30 mL/min.⁸⁷⁹ Renal artery angiography is the gold standard to identify damage to the renal artery. Measuring the translesional gradient to determine the hemodynamic significance of the stenosis is recommended, especially in multifocal lesions. Identification of other vascular segments affected by the disease and investigation of aneurysms and dissections are recommended⁸⁸⁰ (Figure 15.2).

Isolated angioplasty is the recommended procedure, with stenting in case of complications (arterial rupture or dissection). In the absence of contraindications, continuous antiplatelet therapy with acetylsalicylic acid at 75 to 100 mg/day is indicated to prevent thrombotic complications, and dual antiplatelet therapy may be used for a short period of four to six weeks.⁸⁸¹ Doppler ultrasound of renal arteries 30 days after angioplasty is recommended, repeated every six

months for the first two years and annually afterward, to detect restenosis.⁸⁷⁹ As a matter of course, all patients should be included in follow-up, and optimally undergo yearly clinical and imaging assessments.

15.3.1. Coarctation of the Aorta

Coarctation of the aorta is a congenital anomaly leading to narrowing of the aorta, usually juxtaductal, proximal to the ductus arteriosus or ligament. It is usually underdiagnosed, with diverse clinical presentation, from early symptoms at birth (severe) to asymptomatic into adulthood,⁸⁸² depending on the site and severity of the coarctation as well as the frequent presence of other congenital heart diseases impacting prognosis.⁸⁸³ The definition of significant coarctation requires pre- and post-coarctation pressure gradient > 20 mm Hg. Clinical suspicion is based on symptoms (resistant or refractory HT, epistaxis, headache and weakness of the legs on exertion, manifestations of HF, angina, aortic dissection, or intracerebral hemorrhage) and physical examination (hypertension in the upper limbs [ULs] with SBP at least 10 mm Hg higher in the brachial artery than in the popliteal artery; absent or diminished pulse in lower limbs [LLs]; interscapular and thoracic systolic murmur).¹⁶⁴ Diagnosis is based on imaging examinations: chest X-ray (thoracic aorta with pre- and post-stenosis dilations, costal corrosion); echocardiogram, the primary screening examination (posterior protrusion, expanded isthmus, transverse aortic arch, and high-velocity continuous jet through the coarctation site); CT or MNR angiography⁸⁸⁴ in case of poor acoustic window. The MNR is considered the gold standard for assessment and post-intervention follow-up and, in young individuals, does not require invasive preoperative angiography, indicated when other imaging methods cannot provide visualization of the coarctation, and in older individuals who may have CAD. Intervention treatment includes angioplasty, implantation of vascular endoprosthesis, or open surgery (hypoplasia of the aortic arch and/or need for coarctation resection). The perioperative mortality rate is very low and prognosis is relatively good, though patients with coarctation of the aorta have higher and earlier incidence of CV disease than the general population and require continuous monitoring.⁸⁸⁵ The BP response to intervention treatment depends on the duration of AH prior to surgery and the patient's age.⁸⁸⁶ Though many lower BP after an invasive procedure, most develop exercise-induced HT. The drugs of choice for both the preoperative period and residual BP after surgery are beta-blockers (BBs) and angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II AT1 receptor blockers (ARBs).^{885,887} Renin-angiotensin-aldosterone system blockers (SRAA) should be used with caution in the preoperative period in order to avoid major decreases in blood flow distally from the coarctation, which would trigger acute kidney damage.^{885,887}

15.3.2. Obstructive Sleep Apnea (OSA)

15.3.2.1. Concept and Epidemiology

OSA is a clinical condition characterized by the intermittent collapse of the upper airways during sleep, causing total (apnea)

and partial (hypopnea) obstructions.⁸⁸⁸ Respiratory pauses lead to greater respiratory efforts and lower intrathoracic pressure, which cause increased left ventricle transmural pressure, cyclical dips in oxygen saturation (intermittent hypoxia), hypercapnia (usually mild), and sleep fragmentation.⁸⁸⁹ The mechanisms involved with HT include activation of the sympathetic nervous system, systemic inflammation, increased production of reactive oxygen species, and endothelial dysfunction, among others.⁸⁸⁹

Traditionally, OSA severity is determined by adding up apnea and hypopnea events (known as apnea-hypopnea index [AHI]), as determined by objective sleep testing: AHI < 5 events/h: no OSA; AHI 5-14.9 events/h: mild OSA; AHI 15-29.9 events/h: moderate OSA; AHI ≥ 30 events/h: severe OSA. The prevalence of OSA in the general population is high, depending on the diagnostic criteria adopted. In adults, it affects approximately 9.6% of women and 24.8% of men.⁸⁹⁰ In hypertensive patients in general, it is estimated that 56% suffer from some degree of OSA.⁸⁹¹⁻⁸⁹⁴ For those with resistant HT, the prevalence is estimated at > 60% and is likely the most frequent cause associated with secondary HT,⁸⁹⁵ though it does not mean OSA is the only cause in most cases. Though there is evidence that normotensive OSA patients progress to higher incidence rates of HT regardless of other risk factors,^{896,897} in clinical practice, OSA frequently arises in previously hypertensive individuals. However, this in no way minimizes the importance of OSA: there is evidence that the association between OSA and HT is linked to higher rates of end-organ damage compared to hypertensive patients without OSA.^{895,896}

15.3.2.2. Clinical Presentation and Screening of OSA in Hypertension

In the general population, some predisposing factors and clinical signs and symptoms should be assessed during examination and may reinforce the clinical suspicion of OSA⁸⁸⁸ (Chart 15.5). OSA prevalence rates are two to three times higher in men than in women, but is also common in the latter group, especially after menopause.

However, many of these signs and symptoms may be less prominent in HT. For instance, daytime sleepiness is often absent in HT, especially in patients with resistant HT.⁸⁹⁹ Screening surveys for OSA in the general population perform poorly, especially in resistant HT patients.⁹⁰⁰⁻⁹⁰³ It should be mentioned that some findings in BP patterns may help screen for patients with OSA. Recent data suggest that changes in nighttime BP dipping, especially the ascending waveform (mean BP during sleep higher than when awake), increase the odds of OSA three to four times.⁹⁰⁴

15.3.2.3. Impact of Treatment of OSA on BP

The treatment of choice for OSA, especially in moderate to severe cases, is the use of a continuous positive airway pressure (CPAP) device.⁸⁸⁸ Mandibular advancement, oropharyngeal exercises, positional therapy, and surgery can be used in less severe and select cases of OSA.⁹⁰⁵

Overall, treatment of OSA has a modest impact on BP (around 2 to 3 mm Hg).⁹⁰⁶ These results are partially justified by the following factors: 1) many trials and meta-analyses combine controlled and uncontrolled hypertensive and normotensive participants;⁹⁰⁶ and 2) adherence to CPAP use is not always adequate.⁹⁰⁶ Randomized trials have shown that the impact of OSA treatment on BP is greater for RHT patients (circa 5 mm Hg, on average), but generally do not lead to blood pressure control them.⁹⁰⁷⁻⁹⁰⁹ A study found that the presence of altered nighttime dipping was a predictor of better response from CPAP use in lowering BP for OSA patients.⁹¹⁰ Another poorly understood finding is that individuals afflicted with excessive sleepiness have greater decreases in BP.⁹¹¹ Chart 15.6 details a few predictors of better blood pressure response to CPAP use.⁹¹¹

15.3.2.4. Antihypertensive Treatment in Hypertensive Patients with OSA

Thus far, there is no conclusive evidence than any particular class of antihypertensive medication is preferable for hypertensive patients suffering from OSA.⁹⁰⁵ A few aspects deserve to be highlighted here:

In general, the effect of antihypertensives seems to be more effective than CPAP use on lowering BP, but combining CPAP use and an antihypertensive has additional benefits, especially for nighttime BP.⁹¹²

Though more effective than CPAP alone, pharmacological treatment for HT usually does not improve the severity and symptoms of OSA. Even the effect of some diuretics and salt restriction on OSA severity (based on the theory that overnight rostral fluid shift favors upper airway collapsibility)⁹¹³ has a very modest impact on the severity of OSA.^{914,915}

15.4. Endocrine Causes

15.4.1. Primary Hyperaldosteronism (PH)

HT accompanied by suppressed plasma renin activity (PRA) and increased aldosterone excretion characterizes primary aldosteronism.⁹¹⁶ PH was considered a rare form of secondary HT (1%), but may currently be found in 22% of RHT patients.^{917,918} Gordon et al. found the incidence of PH in the primary hypertensive population to range from 5 to 15%, and to probably be approximately 12%.⁹¹⁹ Bilateral cortical adrenal hyperplasia is the most frequent cause of PH (50-60%), while aldosterone-producing adenomas (APA) account for 40% of PH cases.⁹²⁰ Aldosterone-producing cortical adrenal carcinomas and unilateral cortical adrenal hyperplasia are less frequent causes of PH.

The main confirmatory tests for PH are listed in Chart 15.7,⁹²⁰⁻⁹²⁴ while the diagnostic investigation flow chart can be found in Figure 15.3.

The most accurate imaging examination is the thin-slice CT, and MR provides no advantages. The goal of adrenal venous catheterization with concurrent blood sampling for aldosterone and cortisol is to identify the source of aldosterone secretion, and is considered the most accurate test to differentiate PH subtypes. It is recommended for patients with normal adrenal glands or bilateral abnormalities in CT scans.

In addition, adrenal venous catheterization is indicated in patients with small adrenal nodules (< 1.5 cm) and age 40 or older at HT diagnosis, as it may be a nonfunctioning adenoma.⁹²⁰⁻⁹²⁴ The method is invasive and depends on the radiologist's experience. The treatment of choice for APA is unilateral adrenalectomy, preferably laparoscopic, unless contraindicated.

In hyperplastic HT, treatment consists of mineralocorticoid antagonists (spironolactone 50 to 400 mg/day).⁹²⁰⁻⁹²⁴ The primary target of pharmacological treatment should be the renin blockade (in addition to blood pressure control and correcting hypercalcemia) in order to lower the cumulative incidence of cardiovascular events.⁹²⁵

15.4.2. Pheochromocytoma

Pheochromocytomas (PHEO) are catecholamine-secreting chromaffin-cell tumors of the sympathetic adrenomedullary axis.⁹²⁶ Ten to 15% are extra-adrenal (paragangliomas), 10% are bilateral, and 15 to 20% are malignant (from 2 to 50%, depending on genetic defect).⁹²⁷ The incidence rate for pheochromocytoma and paraganglioma is 0.6 cases per 100 000 persons-year.

The symptoms are the classic triad: headaches, profuse sweating, and palpitations with RHT/RfHT or paroxysmal HT (50%; hypertensive crises alternating with normal BP periods). The simultaneous presence of the classic triad and a hypertensive crisis has 89% diagnostic sensitivity and 67% diagnostic specificity.⁹²⁶

Pheochromocytoma or paraganglioma diagnosis requires confirmation of excess catecholamine secretion and documenting the anatomy of the tumor. Laboratory diagnosis is based on blood and urine catecholamine metabolite levels. Free plasma metanephrine (metanephrine and normetanephrine) has 97% sensitivity and 93% specificity,⁹²⁶ (LR: I; LE: A), but because of its higher cost, urine metanephrine isolated or associated with urine catecholamines (epinephrine, norepinephrine, and dopamine) is indicated. Though less sensitive, high urine catecholamine values (> 2 times the upper bound) indicate high diagnostic probability.²⁴² Urine metanephrine levels are more sensitive than urine catecholamine and vanillylmandelic acid for PHEO and paraganglioma diagnoses (ungraded recommendation).⁹²⁸

In acute stress situations (acute illness, sepsis, AMI, decompensated HF) and the use of tricyclic antidepressants, antipsychotics agents, and levodopa, among others, it may be accompanied by increased catecholamine levels (usually < 2x the upper limit of normality). The medication should be suspended two weeks before sample collection to prevent false positives. The imaging tests to locate adrenal tumors are CTs (preferably; LR: 2; LE: B) and MNRs (hypersignal at T2 for PHEO), with 89% and 98% sensitivity, respectively.⁹²⁹ An MRI is superior in the identification of paraganglioma or lymph node metastases (LR: I; LE: B). Whole-body scintigraphy using ¹²³I-MIBG or ⁶⁸Ga DOTATE-PET-CT is very effective at locating PHEOs and paragangliomas, metastases or multiple chromaffin-cell tumors (LR: IIa; LE: C).^{930,931}

The preferential treatment is minimally invasive surgery (LR: I; LE: B), and preoperative preparation should include alpha-

1-blockers (doxazosin or prazosin) and adequate hydration with increased oral sodium intake for at least 2 weeks prior to surgery.⁹³² The chronic pharmacological treatment includes alpha1-blockers, BBs (only after beginning alpha1-blockers, in the presence of symptomatic tachycardia), CCBs, ACEIs, and central action agonists.⁹³² The paroxysmal hypertensive crisis of PHEO is an emergency, and should be treated with sodium nitroprusside or injectable phentolamine and volume replacement, if necessary.⁹²⁶

Total and early removal of the neoplasm usually determines total remission of symptoms and cure of AH, in addition to preventing metastatic disease.^{927,929} For malignant PHEO with unresectable metastases, systemic therapy with MIBG-131 is indicated. Cytotoxic chemotherapy is indicated in case of disease progression after high cumulative dose of MIBG-131 or in case of metastasis without MIBG uptake. Zoledronic acid is indicated to fight pain and lower fracture risk in patients with bone metastases.^{927,929} Clinical, biochemical and radiological follow-up of patients is essential to detect malignant recurrences or metastases as well as other tumors in familial syndromes.²⁴²

15.4.3. Hypothyroidism

The clinical signs of hypothyroidism are usually nonspecific, including fatigue, sleepiness and weight gain (mild in most cases). Patients with hypothyroidism have low levels of free thyroxine (T4) and high levels of thyroid-stimulating hormone (TSH), both screening tools for the condition (LR: IIa; LE: B).⁹³³ In subclinical hypothyroidism, free T4 is normal and TSH is elevated. In hypothyroidism, there is higher risk of diastolic HT.⁹³⁴ Hypothyroidism increases vascular resistance and extracellular volume, but BP increases are usually mild (< 150/100 mm Hg).

15.4.4. Hyperthyroidism

Hyperthyroidism increases cardiac output due to increased peripheral oxygen consumption and increased cardiac contractility.⁹³⁵ Systolic HT is common, but HT prevalence depends on the severity of hyperthyroidism. Atrial fibrillation occurs in 10 to 20% of hyperthyroidism patients, and is more frequent in patients age 60 and over.⁹³⁶ The most prominent clinical conditions are Graves' disease (palpitations, weight loss, exophthalmos, goiter, tremors of the extremities, warm skin, and heat intolerance, among other symptoms) or toxic adenoma, which may be more oligosymptomatic in older individuals with toxic multinodular goiters. Diagnosis is based on free thyroxine (T4) and thyroid-stimulating hormone (TSH) levels (LR: IIa; LE: B). usually, free T4 is high and TSH is suppressed.⁹³⁷ In subclinical hyperthyroidism, free T4 is normal and TSH is suppressed. The presence of TSH antireceptor antibodies is diagnostic for Graves' disease, but may be absent in approximately 10% of cases.

15.4.5. Primary Hyperparathyroidism

The frequency of HT in patients with primary hyperparathyroidism ranges from 10 to 60%.⁹³⁸ Most patients with primary hyperparathyroidism are asymptomatic, while the rest

may present with polyuria, polydipsia, osteoporosis, constipation, renal calculi, and HT. The mechanisms involved in HT are undefined, and there is no direct correlation between PHT levels and calcemia with severity of HT. In primary hyperparathyroidism, HT becomes more severe with impaired renal function due to hypercalcemia. Laboratory investigation involves testing calcemia (total and/or ionized calcium), phosphorus, PTH, and 24-hour urine calcium.⁹³⁹ Vitamin D levels (especially if < 20 ng/dL) should also be measured and supplemented to rule out secondary hyperparathyroidism and vitamin D deficiency from normocalcemic primary hyperparathyroidism.

15.4.6. Cushing's Syndrome

Iatrogenic Cushing's syndrome (from the use of exogenous corticoids) is relatively common, unlike endogenous Cushing's syndrome, which is rare. Among endogenous causes, Cushing's syndrome (ACTH-secreting pituitary adenoma) is responsible for 85% of cases, while 15% are caused by adrenal hyperplasia or tumors (ACTH-independent causes). HT can be found in 75-80% of Cushing's syndrome patients. The mechanisms of HT are the cortisol-enhanced vasopressor effect of catecholamines, the effect of cortisol on mineralocorticoid receptors, and RAAS activation through increased liver production of angiotensinogen. Laboratory diagnosis of hypercortisolism uses baseline cortisol (useful to rule out exogenous use of dexamethasone or betamethasone), midnight salivary cortisol, and 24-h urinary cortisol, in addition to the dexamethasone suppression test (take 1 mg dexamethasone at 11 PM and measure serum cortisol level at 7-8 AM of the following morning). Radiological investigation should be based on adrenal CT scans or pituitary MRI for ACTH-dependent hypercortisolism. Imaging examinations should only be performed after clinical and laboratory diagnosis of hypercortisolism. Treatment of endogenous Cushing's syndrome depends on the etiology of the hypercortisolism. It can be managed surgically or with medications.⁹⁴⁰

15.4.7. Obesity

Excessive visceral fat is accompanied by major hormonal, inflammatory and endothelial abnormalities.⁹⁴¹ All these mechanisms trigger a cascade of cytokine and adipokine release, increasing insulin resistance and determining RAAS and SNS hyperactivity, causing water and sodium retention and, consequently, HT and increased CV and renal risk. Countless studies have shown the close association between increased BP and weight gain. Adopting a weight loss strategy (see Chapter 8) is a key recommendation to lower BP and decrease CV risk as well as associated diseases, such as OSA.^{942,943}

From a practical standpoint, though it has been criticized for ignoring race/ethnicity, age, sex, and other parameters, obesity is categorized according to BMI (kg/m²) as class 1, BMI 30 to < 35; class 2, BMI 35 to < 40; and class 3, BMI ≥ 40. Measuring abdominal circumference can also help diagnose central obesity. Further studies, such as bioimpedance and more accurate and very expensive imaging examinations may be performed, especially in clinical trials, such as dual-energy x-ray absorptiometry scanning (DEXA), CT and MNR.⁹⁴⁴⁻⁹⁴⁵

15.4.8. Acromegaly

In approximately 98% of cases, sporadic or familial acromegaly is caused by growth hormone-secreting pituitary adenomas. Excess growth hormone (GH) stimulates hepatic secretion of insulin-like growth factor-1 (IGF-1), the cause of most clinical manifestations.

They are more frequent between ages 30 and 50 and can be divided into microadenomas (smaller than 1 cm) and macroadenomas (1 cm or larger). The second kind accounts for over 70% of tumors causing acromegaly. HT can occur in approximately 30% of cases and is multifactorial in nature, with a hydrosaline retention component, direct antinatriuretic effect of GH, RAAS and hyperactivity, and endothelial dysfunction, in addition to dysglycemia, left ventricular hypertrophy (LVH) and OSA. Other symptoms can be found in Chart 15.2.⁹⁴⁷

Laboratory assessment begins with serum IGF-1 and GH levels (LR: I; LE: B). Very low GH levels (below 0.4 ng/mL) rule out acromegaly, especially when associated with normal IGF-1 serum levels. GH level after glucose overload (75 g) can demonstrate the nonsuppression of GH secretion (LR: I; LE: B). IGF-1 levels and GH suppression testing after glucose overload are also employed to evaluate response to treatment. Sella turcica MNR is the best imaging examination to identify the tumor and, if contraindicated, may be replaced by a sella turcica CT scan (LR: IIa; LE: B).⁹⁴⁶⁻⁹⁴⁸ Acromegaly treatment may involve surgical procedures, radiotherapy, and pharmacological treatment with somatostatin analogs, with octreotide, lanreotide, and cabergoline available in the Brazilian Unified Health System (SUS).⁹⁴⁹

15.5. Pharmacological Causes, Hormones, and Exogenous Substances

It is a relatively common and underestimated cause of worsening HT or even its induction, frequently circumventable or reversible. A full history of all medications, drugs and supplements in use should be taken for all hypertensive patients.⁸⁵⁹

Hypertensive mechanisms vary widely and may be multifactorial, such as volume retention (glucocorticoids, ketoconazole, oral contraceptives, androgen therapy, nonsteroidal anti-inflammatory drugs [NSAID]), sympathetic hyperactivity (decongestants, amphetamines, monoamine oxidase inhibitors [MAOIs], antidepressants, other psychiatric medications, cocaine, calcineurin inhibitors), and RAAS hyperactivity (immunosuppressants).⁹⁵⁰ Good clinical practice dictates that hypertensive patients should be informed when combining medications can lead to worse blood pressure control.⁹⁵¹

Angiogenesis inhibition via endothelial vascular growth factor inhibition is an antineoplastic strategy applied in various oncology settings. Blood pressure increases, even acute ones, are a common side effect.⁹⁵² The mechanisms involved are the activation of the endothelin system, endothelial dysfunction, and capillary rarefaction. It is recommended that blood pressure be below 140/90 mm Hg before initiating this form of treatment and that BP monitoring continue throughout the therapy.⁹⁵³ (see Chart 15.8).

Guidelines

Key Takeaways

In the absence of clinical signs suggestive of secondary hypertension in adults, the indications for additional assessment are resistant hypertension and early- or late-onset hypertension and/or sudden BP increase.

Major causes of secondary hypertension, both endocrine and nonendocrine, signs, and diagnostic and screening methods can be found in Table 15.2.

The most frequent cause of secondary hypertension is primary aldosteronism (PA). The aldosterone/renin ratio is the best initial test to determine the need for additional PA assessments. Paroxysmal HT with triad consisting of headaches, sweating, and palpitations is found in pheochromocytoma.

Renal artery stenosis should be investigated when creatinine levels increase $\geq 50\%$ after ACEI or ARB use. Recent-onset severe HT occurs in individuals > 55 years old with abdominal murmur and a > 1.5 cm size difference in the contralateral kidney. HT is severe in patients suffering from atherosclerosis or recurrent pulmonary edema. In young adults with severe HT, fibromuscular dysplasia of the renal artery should be considered.

Other causes of secondary hypertension require more specific diagnostic methods, expert knowledge, and experience in interpreting results. Treatment should be directed by specialists from referral centers.

Chart 15.1 – Signs of secondary hypertension

1	Stage 3 hypertension before age 30 or after 55
2	Resistant or refractory hypertension
3	Use of exogenous hormones, medications or other substances that may increase BP (see Chart 15.7)
4	Pheochromocytoma triad: palpitations, sweating, and headaches
5	Signs of obstructive sleep apnea
6	Typical facies or phenotype for diseases that progress to hypertension
7	Presence of bruits in arterial areas or abdominal masses
8	Asymmetry or absence of LL pulse
9	Spontaneous or diuretic-induced severe hypokalemia (< 3.0 mEq/L)
10	Abnormal urine test (glomerular hematuria (dysmorphic) or presence of albuminuria/proteinuria), lower estimated GFR, increased serum creatinine, or alterations in renal imaging

Chart 15.2 – Major endocrine and nonendocrine causes of secondary HT, signs, and diagnostic screening

Clinical findings	Diagnostic suspicion	Additional findings
Nonendocrine causes		
Edema, anemia, anorexia, fatigue, high creatinine and urea, and changes in urinalysis or imaging examinations	Renal parenchymal disease	Creatinine and eGFR calculation (I: B), renal US, urinalysis (I: C) for dysmorphic proteinuria/hematuria. Albuminuria or proteinuria/urine creatinine ratio where indicated (LR: I; LE: B)
Sudden-onset HT or apparently unexplained worsening before age 30 or after 55, resistant or refractory HT or MHT, abdominal murmur, sudden APE, unexplained alteration in renal function or caused by RAAS blockers, kidney asymmetry > 1.5 cm	Renal artery stenosis	Renal Doppler US with flow velocity measurement and resistivity index (screening, but observer-dependent) (LR: I; LE: B) and/or captopril radioisotope renography (LR: III; LE: C), MNR angiography (eGFR > 30 mL/min, BOLD or digital subtraction) (LR: I; LE: B) or spiral CT (eGFR > 60 mL/min (LR: I; LE: B) Gold standard: conventional renal arteriography (LR: I, LE: A)
Higher frequency in men or postmenopausal women, snoring on most nights, sleep fragmentation with respiratory pauses or choking, excessive daytime sleepiness, nonrestorative sleep, fatigue, nocturia, morning headaches, MS	Obstructive sleep apnea (OSA)	Surveys have low accuracy for screening purposes Gold standard: polysomnography or home respiratory polygraphy. AHI < 5 events/h: no OSA; AHI 5-14.9 events/h: mild OSA; AHI 15-29.9 events/h: moderate OSA; AHI ≥ 30 events/h: severe OSA
Weakness in LLs, absent pulse or diminished amplitude, HT with SBP 10mm Hg > in ULs over ULs, interscapular and thoracic systolic murmur	Coarctation of the aorta	Chest X-ray, screening echocardiogram CT angiography of the chest or, preferably, aortic MNR (gold standard) Invasive angiography, only when additional data are required
Endocrine causes		
RHT or RfHT and/or with hypopotassemia (non obligatory) and/or with adrenal nodule	Primary hyperaldosteronism (hyperplasia or adenoma)	Aldosterone measurements (>15 ng/dL) and plasma renin activity/concentration; aldosterone/renin ratio > 30 Confirmatory testing (see Chart 15.7) Imaging examinations: thin-slice CT or MNR. Selective aldosterone and cortisol adrenal sampling to identify subtype, when indicated (LR: I; LE: B)
Paroxysmal HT with triad consisting of headaches, sweating, and palpitations	Pheochromocytoma and paragangliomas	Free plasma metanephrines and/or urinary fractionated metanephrines (LR: I, LE: A). CT (LR: IIa, LE: B) (screening), MNR (LR: I; LE: B) and scintigraphy (LR: IIa, LE: C) where indicated
Fatigue, weight gain, hair loss, diastolic HT, muscle weakness, sleepiness	Hypothyroidism	Screening: TSH and free T4 (LR: I, LE: B)
Increased sensitivity to heat, weight loss, tachycardia/palpitations, exophthalmos, hyperthermia, hyperreflexia, tremors, goiter	Hyperthyroidism	Screening: TSH and free T4 (LR: I; LE: B)
Renal lithiasis, osteoporosis, depression, lethargy, muscle weakness or spasms, thirst, polyuria, polydipsia, constipation	Hyperparathyroidism (hyperplasia or adenoma)	Total and/or ionized calcium, phosphorus, PTH, 24-hour urine calcium and vitamin D level (LR: I; LE: B)
Weight gain, decreased libido, fatigue, hirsutism, amenorrhea, moon face, "buffalo hump", purple striae, central obesity, hypopotassemia	Cushing's syndrome (hyperplasia, adenoma and excess secretion of ACTH)	Baseline cortisol, midnight salivary cortisol, 24-h urinary free cortisol, and betamethasone or dexamethasone suppression test (take 1 mg dexamethasone between 11 PM and midnight and measure serum cortisol level at 7-8 AM of the following morning). CT, MNR (LR: I; LE: B)
Increased visceral or central fat	Obesity Class 1: BMI 30 to < 35 kg/m ² Class 2: BMI 35 to < 40 kg/m ² Class 3: BMI ≥ 40 kg/m ²	BMI (weight in kg/height in m ²) and abdominal circumference (> 102 cm in men and 88 cm in women) Imaging examinations: DEXA (gold standard), CT, MNR (clinical trials) (LR: I; LE: B)
HT in up to 30% of cases, in addition to diabetes, LVH, and OSA. Other symptoms: visual defects, cranial nerve palsy, headaches, macroglossia, growth of feet and hands, soft tissue hypertrophy, macroglossia, musculoskeletal complications	Acromegaly	IGF-1 (I, B) measurement, GH serum level and GH after oral glucose overload (I, B) Location: sella turcica MNR (preferred) or CT scan

ACTH: adrenocorticotrophic hormone; AHI: apnea-hypopnea index; APE: acute pulmonary edema; BMI: body mass index; BOLD: blood oxygen level-dependent; CT: computed tomography; DEXA: dual-energy x-ray absorptiometry scanning; eGFR: estimated glomerular filtration rate; GH: growth hormone; IGF-1: insulin-like growth factor 1; LVH: left ventricular hypertrophy; MHT: malignant hypertension; MNR: magnetic nuclear resonance; OSA: obstructive sleep apnea; PTH: parathormone; RAAS: renin-angiotensin-aldosterone system; RHT: resistant hypertension; TSH: thyroid-stimulating hormone. LLs: lower limbs; ULs: upper limbs.

Guidelines

Chart 15.3 – Clinical indicators of renovascular hypertension

Onset of hypertension before age 30

Onset of severe hypertension after age 55 associated with chronic kidney disease and congestive heart failure

Hypertension and abdominal murmur

Rapidly progressive and persistent hypertension in previously well-controlled patient

Resistant or refractory hypertension

Hypertensive crisis with end-organ damage (acute renal failure, congestive heart failure, hypertensive encephalopathy, grade 3 and 4 hypertensive retinopathy)

Worse renal function after treatment with renin-angiotensin system blockers

Unexplained renal atrophy, renal asymmetry, or unexplained worse renal function

Acute pulmonary edema

Aboyans et al., 2018.⁸⁶⁷

Chart 15.4 – Recommendations for diagnosis of renovascular disease

Recommendation	LR	LE
Doppler ultrasound of renal arteries (screening), spiral computed tomography, magnetic resonance angiography	I	B
BOLD or digital subtraction angiography may be indicated to confirm diagnosis of renal artery stenosis detected by other methods in patients with high probability of renovascular disease	II B	C
Renal scintigraphy, serum renin before and after captopril and venous renin not indicated for screening renal artery stenosis	III	C

Aboyans et al., 2018.⁸⁶⁷

Chart 15.5 – Frequency of primary risk factors and symptoms/clinical signs suggestive of obstructive sleep apnea (OSA)

Characteristics	Measures
Risk factors	Odds ratio
Overweight vs eutrophic	2.3-3.4
Obese vs eutrophic	4.0-10.5
Male vs female	1.7-3.0
Age (10-year increments)	1.4-3.2
Postmenopausal (for women)	2.8-4.3
Clinical signs and symptoms	Prevalence (%)
Excessive sleepiness, fatigue, or nonrestorative sleep	73-90
Reported snoring most nights	50-60
Respiratory pauses and choking observed by other person	10-15
Nocturia (2 or more times per night)	30
Nighttime gastroesophageal reflux	50-75
Morning headaches	12-18

Adapted from Gottlieb et al., 2020.⁸⁸⁸

Chart 15.6 – Predictors of better blood pressure response to CPAP use

Clinical characteristics
Patients with better adherence to CPAP (usually > 4 hours per night)
Patients with excessive daytime sleepiness
Patients with resistant hypertension
Patients with altered nighttime BP dipping

Chart 15.7 – Confirmatory testing for primary hyperaldosteronism

Test	Procedure	Dosage	Results	Disadvantages
Saline infusion test	Infusion of 2 L of 0.9% saline solution over 4 h (start from 8 to 9:30). In the sitting position, has higher sensitivity for PH diagnosis.	K ⁺ , aldosterone (A), renin (R) at t = 0 and after 4 h.	Sitting: A values > 6.0 to 10 ng/dL at the end of the test are positive. The cutoff value with highest sensitivity/specificity is 6.0 ng/dL. Lying: A values > 6.8 to 10 ng/dL at the end of the test are positive. The cutoff value with highest sensitivity/specificity is 6.8 ng/dL.	Side effects: hypertensive crisis, hypervolemia Contraindicated for patients with severe HT, decompensated HF, renal failure, and severe hypokalemia.
Captopril challenge test	50 mg of captopril orally with patient remaining sitting for 2 h.	A, R, K ⁺ and cortisol at times 0, 1 h, and 2 h.	A > 8.5-13.9 ng/dL or suppression of A > 30%. Subtract percentage cortisol decrease from percentage A decrease.	Side effects: hypotension Safe test, but with low reproducibility. Indicated for patients suffering from renal failure.
Fludrocortisone test	Fludrocortisone 0.1 mg every 6 h for 4 days.	K ⁺ control every 6 h. Measure A and R at 10 h of the 5 th day.	Positive A > 6 ng/dL with suppressed R.	Side effects: Hypertensive crisis, hypervolemia, and hypokalemia. Contraindicated for patients with severe HT, decompensated HF, renal failure, and severe hypokalemia. Considered the gold standard, but must be performed under hospital admission, since it is unfeasible in clinical practice.
Intravenous furosemide test	Administer furosemide 40 mg IV and stimulate 2 hours of walking.	Measure A, R and K ⁺ before and after 2 hours of intermittent walking.	Positive if PRA < 2 ng/mL/h or Renin < 13 uUI/mL.	Side effects: hypokalemia and hypotension. Advantage: well tolerated and easy to perform, ideal for patients with contraindications for sodium overload

A: aldosterone; PH: primary hyperaldosteronism; PRA: plasma renin activity; R: renin.

Guidelines

Chart 15.8 – Medications, hormones, and exogenous legal and illegal substances related to the development or increased severity of HT

MEDICATIONS		MECHANISMS
Immunosuppressants (calcineurin inhibitors)	Cyclosporin and tacrolimus	Increase prostaglandin synthesis and decrease excretion of Na ⁺ , H ₂ O, and K ⁺
Nonsteroidal anti-inflammatory drugs (NSAID) and analgesics	Cyclooxygenase-1 and -2 inhibitors Acetaminophen	Decreased prostaglandins and Na ⁺ and fluid retention
Sympathomimetics	Nasal decongestants (ephedrine, pseudoephedrine, phenylephrine)	Stimulate the central nervous system
Anorexigenic/satiatogenic medications	Amfepramone, sibutramine	Increase norepinephrine secretion
Antidepressants and psychiatric medications	Tricyclics, monoamine oxidase inhibitors (MAOI), lithium, fluoxetine, selegiline, carbamazepine, clozapine, buspirone, duloxetine, venlafaxine, and desvenlafaxine	Increased norepinephrine secretion, causing sympathetic hyperactivity
Antifungal medicines	Ketoconazole, amphotericin B	Fluid retention
Ergot alkaloids	Bromocriptine	
Combination antiretroviral therapy (CART)		
VEGF (vascular endothelial growth factor) antineoplastic inhibitors	Axitinib, bevacizumab, ponatinib, pazopanib, regorafenib, sorafenib, sunitinib	Endothelial dysfunction and lower nitric oxide
EXOGENOUS HORMONES		
Glucocorticoids		Na ⁺ and fluid retention
Human recombinant erythropoietin		Abnormal production and sensitivity to endogenous vasopressor agents, direct vasopressor action, and arterial remodeling
Sex hormones (estrogen-replacement therapy (conjugated estrogens and estradiol; oral contraceptives))		Stimulate angiotensinogen production
Growth Hormone (GH)		Multifactorial
EXOGENOUS SUBSTANCES		
Alcohol		Sympathetic hyperactivity
Amphetamines		Sympathetic hyperactivity
Cocaine		Sympathetic hyperactivity
Plant-based supplements		
Liquorice		
Ginseng		
<i>Ginkgo biloba</i>		

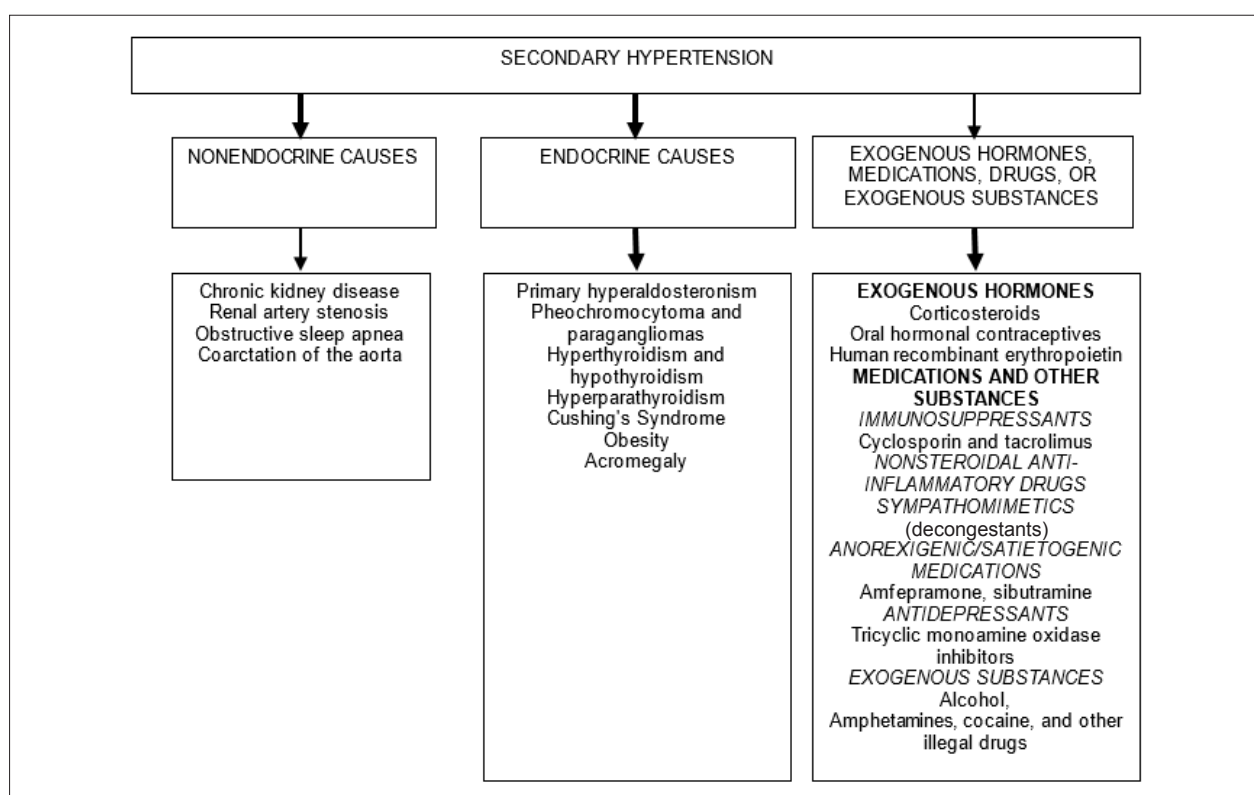


Figure 15.1. – Causes of secondary HT: nonendocrine, endocrine, and due to use of exogenous hormones, medications, drugs, or exogenous substances.

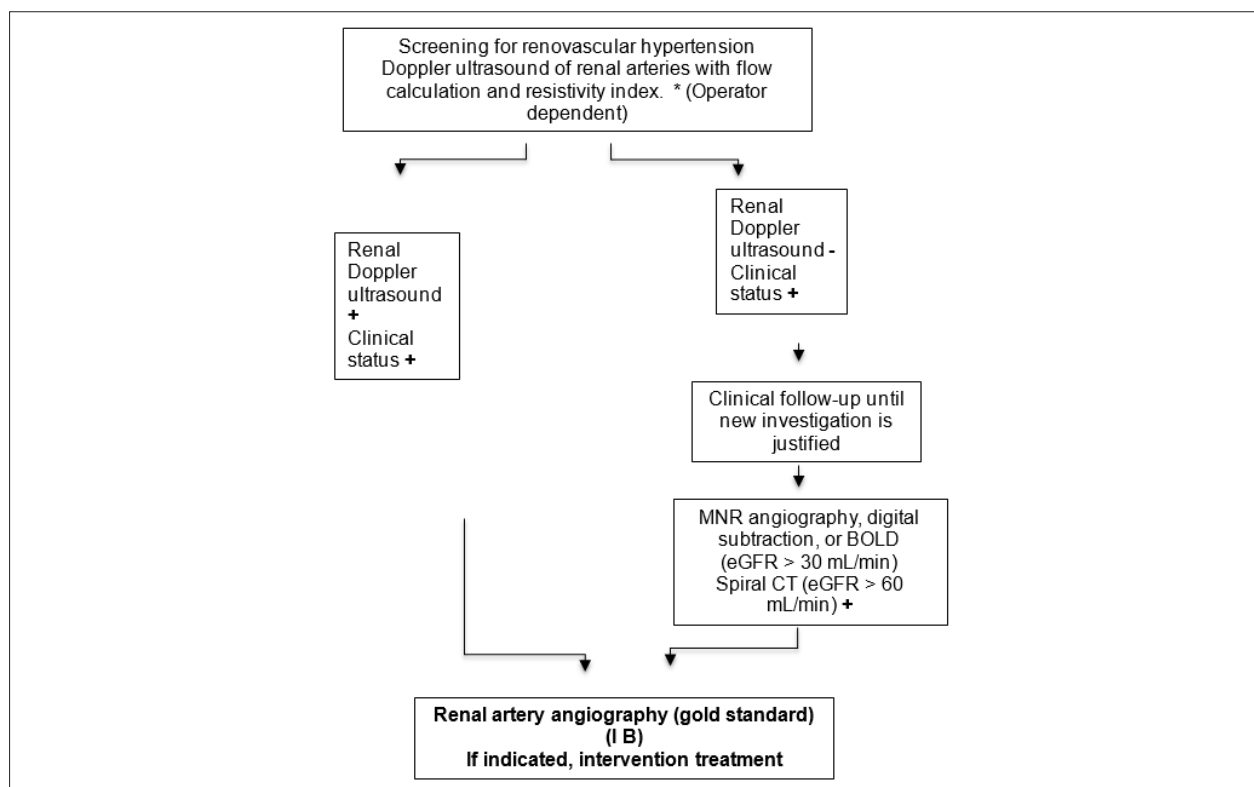


Figure 15.2. – Flow chart for investigation of patient suspected of having renal artery stenosis.

Guidelines

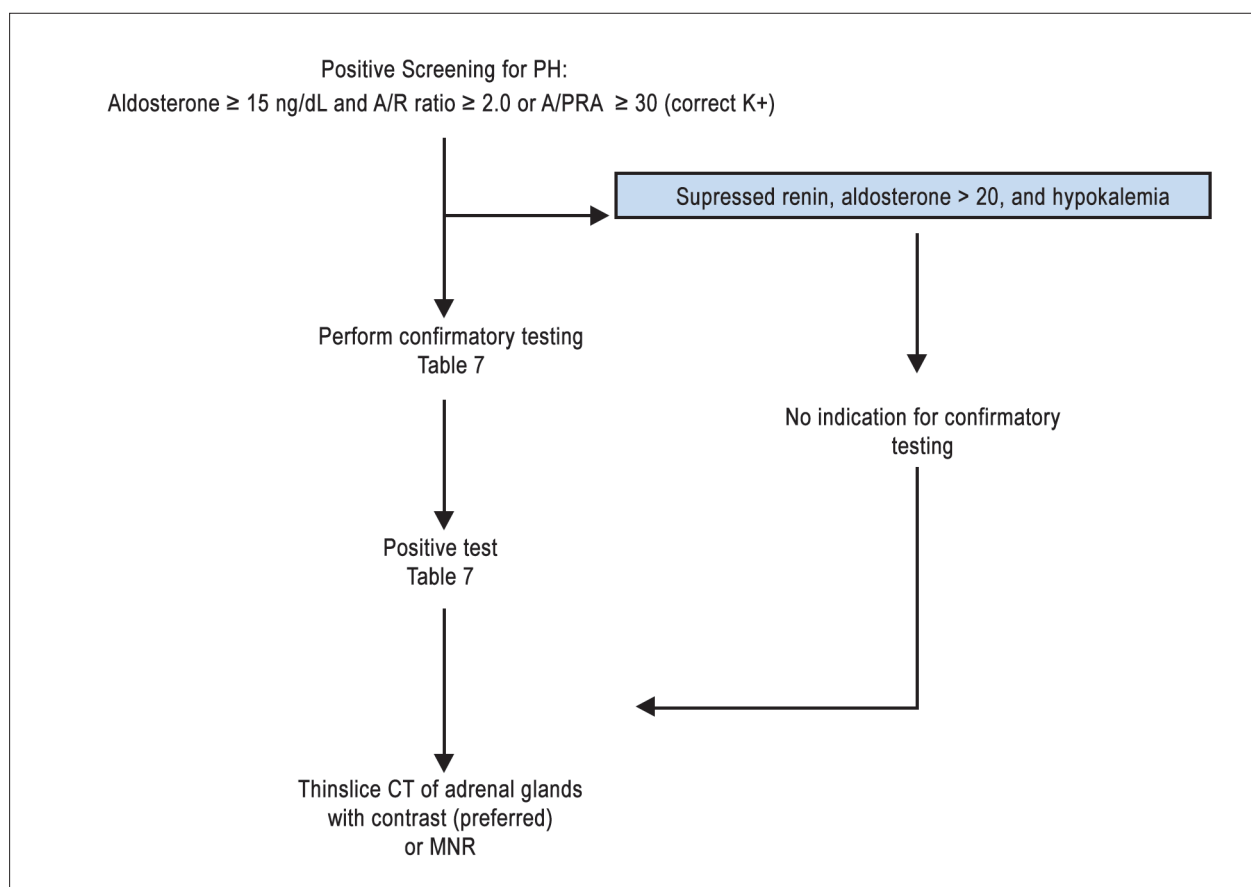


Figure 15.3. – Flow chart of diagnostic investigation of primary hyperaldosteronism.
Adapted from Vilela & Almeida, 2016.³²⁴

16. Resistant And Refractory Hypertension

16.1. Definition and Classification

Resistant hypertension (RHT) is defined as office BP that remains $\geq 140/90$ mm Hg with the use of three or more classes of antihypertensive medications with synergistic action, in maximum tolerated or recommended doses, one of which preferably a thiazide diuretic. When patients require four or more antihypertensive medications to achieve BP control, they are considered resistant but controlled hypertensives (BP $< 140/90$ mm Hg) (Figure 16.1).^{164,504,564,954}

Refractory hypertension (RfHT) is defined as a subgroup of patients with true RHT that maintain uncontrolled BP (BP $\geq 140/90$ mm Hg), even when using four or more antihypertensives, including spironolactone and a long-acting diuretic (Figure 16.1).⁹⁵⁵ Pseudo-resistant hypertension is defined as the failure to control BP related to white coat hypertension, failure at BP measurement, therapeutic inertia, or lack of adherence to prescribed pharmacological and nonpharmacological treatment regimens (Figure 16.2).^{164,504,564,954} Identifying patients with true RHT, therefore, requires ruling out pseudo-resistance and associated conditions (Figure 16.2), making it essential to establish specific approaches.^{164,504,564,954}

16.2. Epidemiology of Resistant Hypertension

In population-based studies, RHT prevalence is estimated at 12 to 15% of the hypertensive population.^{164,504,564,954} In Brazil, the multicenter ReHOT study⁵⁶⁴ found an 11.7% prevalence rate for RHT. RfHT corresponds to 3.6% of resistant hypertensives.¹⁶⁴

The main clinical conditions and characteristics associated with RHT patients can be found in Chart 16.1.^{164,504,564,954,956} Worse prognoses for these patients is especially associated with the following factors: prolonged exposure to high blood pressure levels, end-organ damage, excess mineralocorticoids (aldosterone), and high sodium intake.^{164,504,564,954,956}

16.3. Pathophysiology

Just as the pathophysiology of primary hypertension is multifactorial, multiple factors may also be involved in the genesis of RHT and RfHT. This determines the various degrees of refractoriness to antihypertensive medications (Figure 16.1).

RHT depends more on increased blood volume than RfHT due to persistent fluid retention, increased salt sensitivity, hyperaldosteronism, and renal dysfunction. In addition, the greater expansion of chest plasma, urinary aldosterone concentration, discrete suppression of renin activity⁹⁵⁷ and high plasma aldosterone/renin ratio, as well as high levels of atrial and brain natriuretic peptide (BNP) are found in these individuals.⁹⁵⁸⁻⁹⁶⁰ The ratio between volume and high blood pressure is the primary physiopathological basis shown in several studies^{955,957-960} (Figure 16.3) and justifies the use of diuretic to treat RHT patients.⁹⁶¹

In contrast, RfHT patients predominantly suffer from sympathetic nervous system hyperactivity and greater vascular stiffness.⁹⁶² Higher pulse wave velocity values, indicating

elevated vascular stiffness and higher cytokine levels, such as tumor necrosis factor- α ,⁹⁶³ may mediate vascular damage in refractory hypertensive patients.⁹⁶⁴ Other factors, such as age, obesity, obstructive sleep apnea (OSA), African-American descent, altered adipokines, endothelial dysfunction, and higher metalloproteinase-2 and -9 and adhesion molecule activity, are also involved in the process.^{504,954,895} Gene polymorphisms, especially for RAAS and the endothelial nitric oxide synthase enzyme, have also been linked to RfHT⁹⁶⁵ (Figures 16.4 and 16.5).

16.4. Diagnostic Investigation

Resistant hypertension patients should be treated by specialized HT services, capable of offering a multidisciplinary approach. Diagnostic investigation stands on four pillars:^{341,504,954,966}

- Pseudoresistance: Ruling out improper BP measurement (especially cuff width for obese patients), therapeutic inertia, poor adherence, and use of medications that increase BP (see Chapter 15).^{504,954,967}
- Assessment of cardiovascular (CV) risk factor, end-organ damage (EOD), and established CV disease: Once RHT is confirmed, diagnostic investigation should begin with specific tests, following this guideline for hypertension, to assess EOD impairment and secondary hypertension. The presence of associated comorbidities should be detected in specialized tests and examinations, following clinical suspicion.
- Ambulatory blood pressure monitoring (ABPM) and home blood pressure monitoring (HBPM): The diagnosis of RHT is based on office BP,^{504,954} but out-of-office assessments (ABPM or HBPM) is essential to rule out the white-coat effect and masked hypertension.^{504,954,968} Diagnostic and therapeutic management should be based on ABPM and HBPM levels.^{504,954,968,969} Patients with daytime and/or nighttime high blood pressure levels (true RHT or masked HT) should have their medications adjusted and repeat ABPM afterward.^{504,954,968,969} Patients with controlled BP on ABPM should have their therapy regimen maintained, regardless of the office BP levels. For these individuals, ABPM should be repeated annually or semiannually.^{968,969} HBPM may also be used when available. Although it does not assess the nocturnal period and overestimates blood pressure levels, HBPM achieves moderate agreement on diagnosis, with high specificity and low sensitivity.⁹⁷⁰
- Investigation of secondary causes: Secondary causes are more frequent for resistant than for nonresistant hypertension, and the most prevalent is OSA (80%), followed by hyperaldosteronism (6-23%), renovascular disease (renal artery stenosis) (2.5-20%), and renal parenchymal disease (2-10%).^{504,954,895} Investigating altered thyroid function (1-3%) is also warranted.^{504,954}

16.5. Treatment (Chart 16.2)

16.5.1. Nonpharmacological Treatment

All RHT patients should be directed and encouraged to adopt lifestyle changes⁹⁷¹ (see Chapter 8).

16.5.2. Pharmacological Treatment

The basic principle of pharmacological treatment is the combination of antihypertensive medications that act on most physiopathological mechanisms of BP increases: expanded intravascular volume, sympathetic and RAAS activation and increased peripheral vascular resistance.^{504,954,972} Three-drug treatment should include a thiazide diuretic (DIU), a RAAS blocker (ACE inhibitor or angiotensin II AT1 receptor blocker (ARB)), and long-acting dihydropyridine calcium channel blocker (CCB), at full, well-tolerated doses and adequate intervals. In case of coronary artery disease, heart failure or tachyarrhythmias, a beta-blocker (BB) should replace the CCB in the initial three-drug therapy regimen.

The correct use of DIUs is essential for treating RHT: chlorthalidone (25 mg/day) or indapamide (1.5 mg/day) are the diuretics of choice, as long as the estimated glomerular filtration rate (eGFR) is above 30 mL/min. However, at the time of this writing, only hydrochlorothiazide was available in the Brazilian public health system. In patients with stage 4 or 5 chronic kidney disease or heart failure with fluid retention, loop diuretics (furosemide) should be used instead of thiazides and administered as needed for pressure and volume control. Spironolactone (aldosterone antagonist, 25 to 50 mg/day) is the medication of choice to be added as the 4th drug for patients with high adherence and true RHT.^{564,567}

For spironolactone-intolerant patients, amiloride (5 to 10 mg/day) may be used instead.⁹⁷³

For patients with uncontrolled blood pressure after adding spironolactone to the treatment regimen, BBs (especially those with vasodilatory effect) or centrally acting alpha-antagonists (clonidine)⁵⁶⁴ are the 5th/6th-line medications. If blood pressure control is still out of reach, direct-acting vasodilators (hydralazine and minoxidil) may be used as the 7th option.^{974,975}

ABPM-guided chronotherapy, with at least one antihypertensive medication administered at night (especially RAAS blockers and BBs) improves blood pressure control and reverses nondipper patterns for RHT patients in addition to lowering cardiovascular morbidity and mortality.⁹⁷⁶

Adherence to treatment is key for blood pressure control. However, up to 50% of patients with RHT partially or fully do not adhere to pharmacological treatment.⁹⁷⁷

16.5.3. New Treatments

Various invasive treatments, such as endovascular renal sympathetic denervation, carotid baroreflex activation and modulation therapy, carotid body ablation, and central iliac arteriovenous anastomosis, have not been approved and are not to be used to treat resistant hypertensive patients, except as part of research protocols.^{5,978}

Key Takeaways

Resistant hypertensives are individuals adhering to treatment involving three or more classes of antihypertensive medications in optimized doses who do not progress to controlled blood pressure.

Refractory hypertensives are those adhering to treatment with five or more classes of antihypertensive medications in optimized doses who have uncontrolled blood pressure.

In Brazil, the prevalence of true resistant hypertension is 11.7% (ReHot Study).

Resistant hypertension depends more on volume, while sympathetic hyperactivity predominates in refractory hypertension.

For the three initial classes of medication for resistant hypertension, the keys are using diuretics, blocking the renin-angiotensin-aldosterone system, and using direct-acting vasodilators.

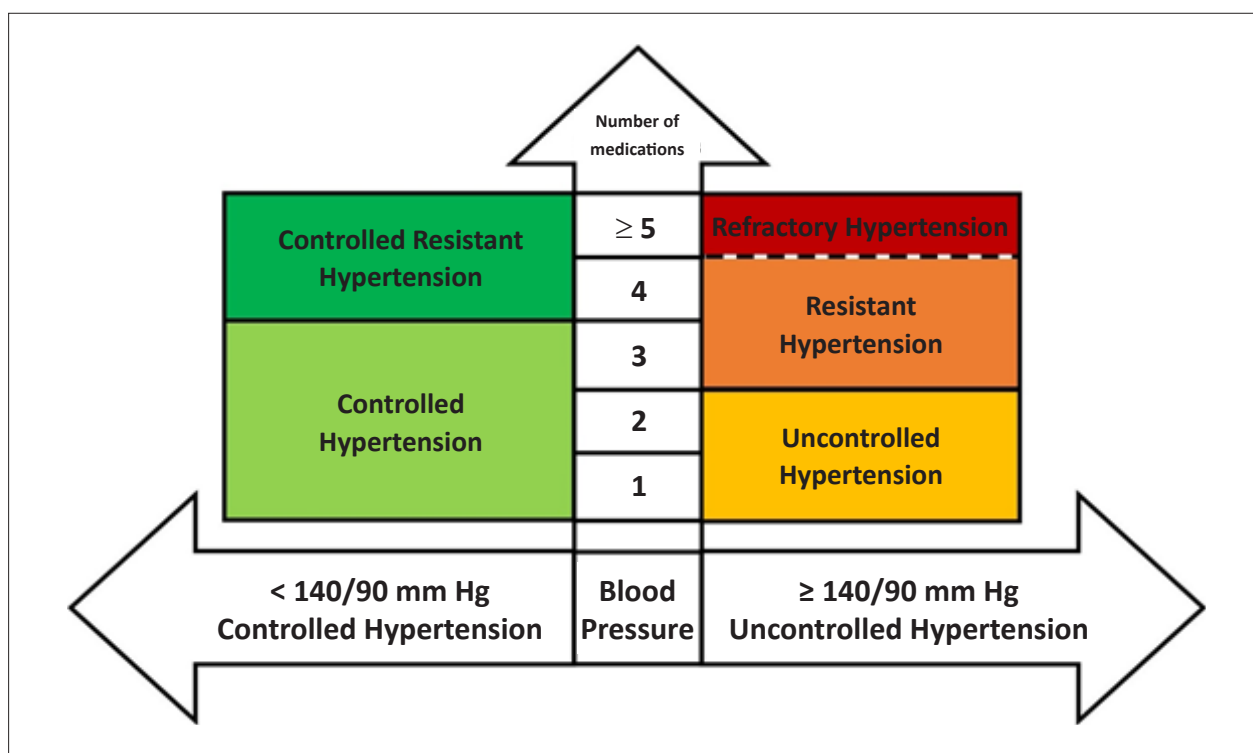


Figure 16.1 – Classification of hypertension according to number of antihypertensive medications and blood pressure control.

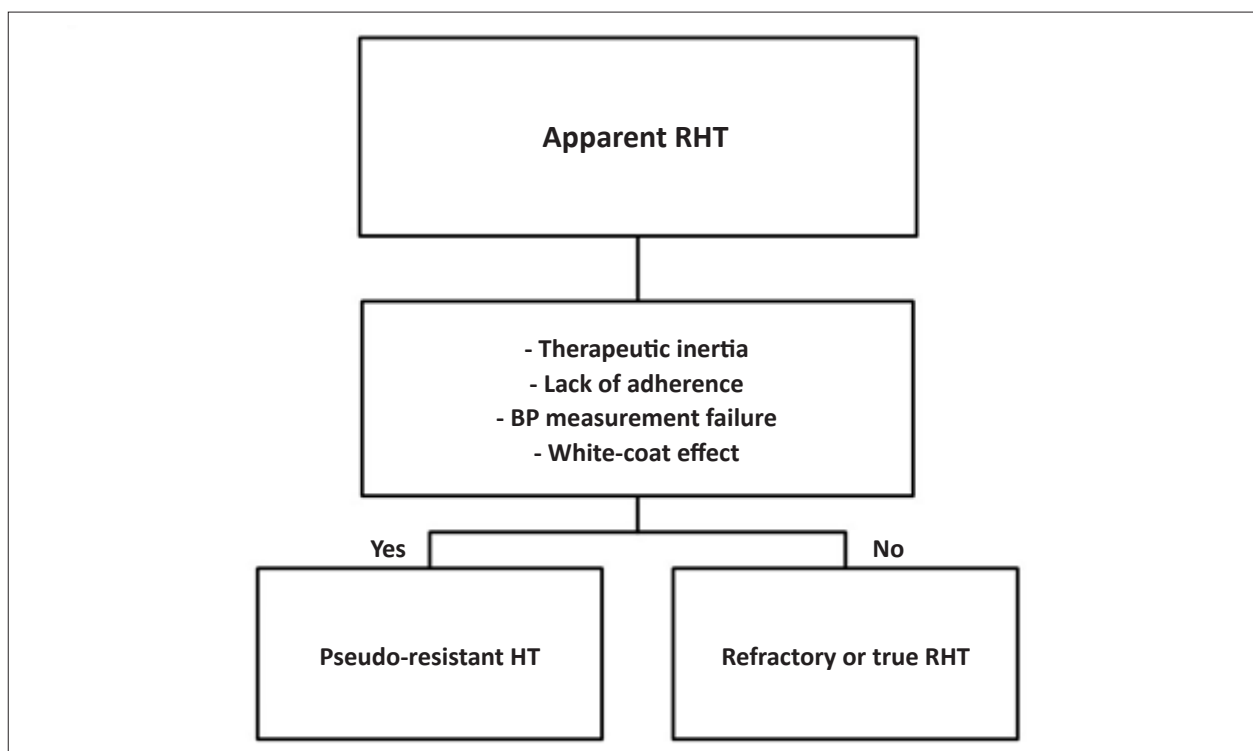


Figure 16.2 – Classification of resistant hypertension.

Adapted from Malachias et al., 2016;¹⁶⁴ Carey et al., 2018;⁹⁵⁴ Yugar-Toledo, 2020;⁵⁰⁴ Krieger et al., 2018;⁵⁶⁴ RHT: resistant hypertension.

Guidelines

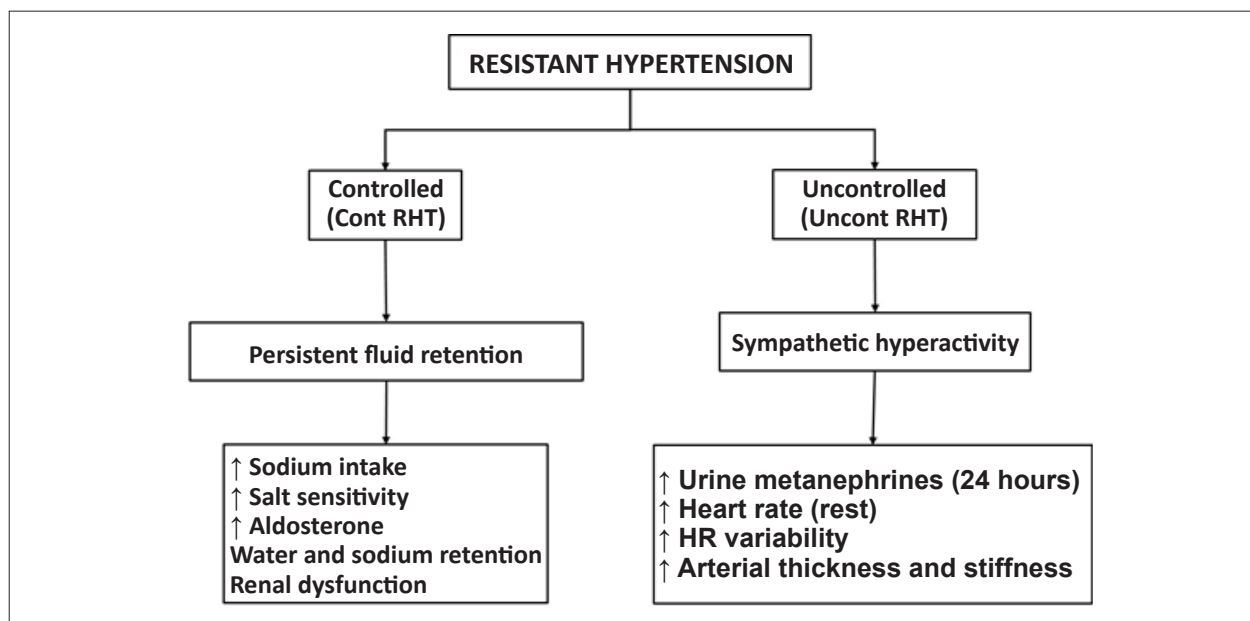


Figure 16.3 – Dominant physiopathological mechanisms in resistant hypertension.

HR: Heart rate. Refractory (uncontrolled) individuals with five classes of antihypertensives are included in the refractory group (3-5%).

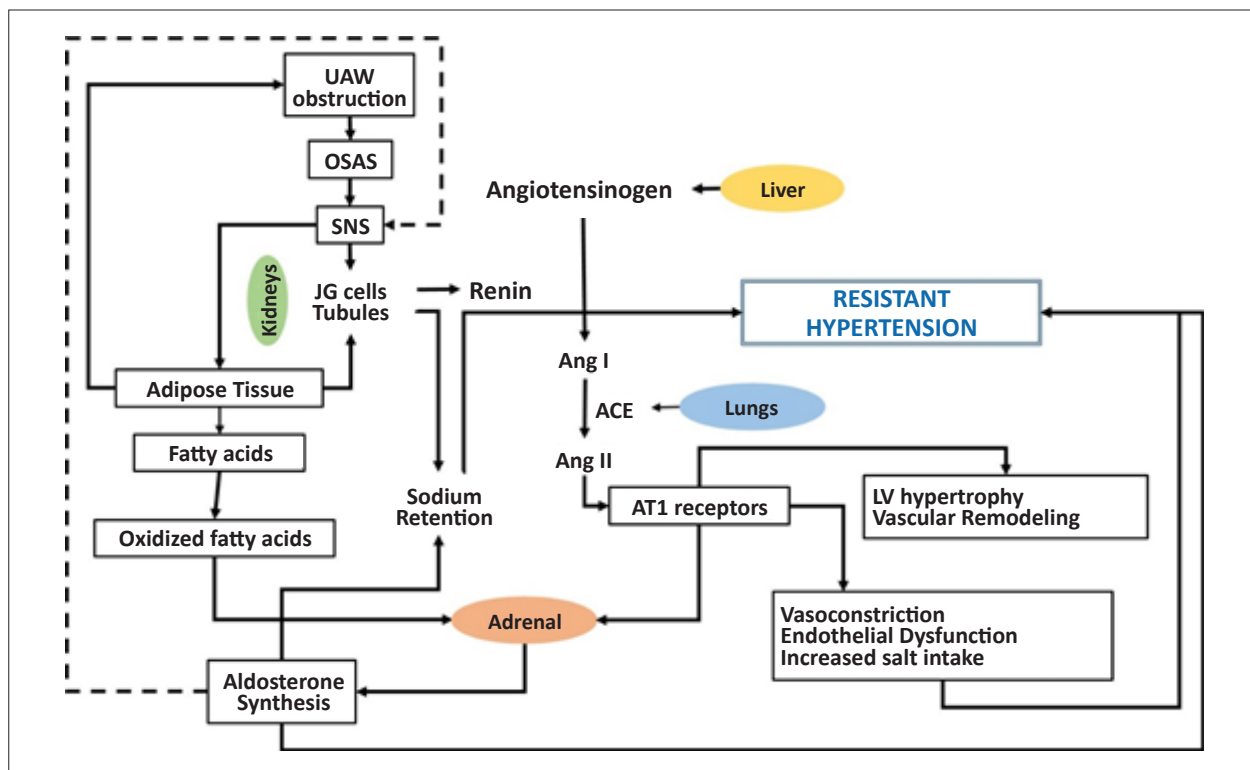


Figure 16.4 – Biomolecular systems measuring imbalance between increased aldosterone synthesis, sodium retention, OSA, increased RAAS activity (AT1 and AT2 receptors) and hypertensive cardiac disease, and increased total vascular resistance, primarily induced by expanded plasma volume (salt retention and excess aldosterone) and sympathetic hyperactivity.

JG cells: juxtaglomerular cells; LV: left ventricle; OSAS: obstructive sleep apnea syndrome; Oxidized FA: oxidized fatty acids; RAAS: renin-angiotensin-aldosterone system; SNS: sympathetic nervous system; UAW: upper airways.

Chart 16.1 – Clinical conditions and characteristics associated with RHT

Clinical characteristics	Associated conditions
• Advanced age • Afro-Brazilians • Obesity • Higher SBP • Nondipper in ABPM • Hypervolemia (even with diuretics) • Excessive salt intake • Sedentary lifestyle • WCE (30%)	• Presence of LVH • DM • Metabolic syndrome • CRF • Albuminuria

Adapted from Malachias et al., 2016;¹⁶⁴ Carey et al., 2018;⁹⁵⁴ Yugar-Toledo, 2020;⁵⁰⁴ Krieger et al., 2018;⁵⁶⁴ Gaddan et al., 2008;⁹⁵⁷ Shimomura, 2013;⁹⁵⁸ ABPM: ambulatory blood pressure monitoring; CRF: chronic renal failure; DM: diabetes mellitus; LVH: left ventricular failure; RHT: resistant hypertension; SBP: systolic blood pressure; WCE: white-coat effect.

Chart 16.2 – Treatment of resistant hypertension

Intervention	LR	LE
Prescribe and encourage LSCs	I	B
Optimize treatment with three medications: hydrochlorothiazide, chlorthalidone or indapamid,* ACEI or ARB, and CCB†	I	B
Add spironolactone as the 4 th medication	I	A
Add a BB and/or clonidine as the 5 th /6 th medication†	IIA	B
Add direct-acting vasodilators sequentially	IIB	C
Prescribe the nocturnal administration of one or more drugs at bedtime	IIB	B
Check and improve adherence to treatment	I	C
Do not use invasive treatment, except in research protocols	III	B

* With glomerular filtration rate ≤ 30 mL/min or CHF, use loop diuretic.

17. Adherence to Antihypertensive Treatment

17.1. Introduction

The primary goal of initiating pharmacological and nonpharmacological antihypertensive treatment is to reduce the morbidity and mortality caused by high blood pressure (BP) levels. Though treatment has proven effectiveness and efficacy, hypertension (HT) control indices are still inadequate in most countries, including Brazil.⁹⁷⁹ A country-level systematic review and meta-analysis performed at the primary care level showed that HT control rates ranged from 43.7% to 67.5%.⁹⁸⁰ There are many reasons for the lack of hypertension control, but one of the most important is the lack of adherence to treatment, which can have various reasons.

17.2. Concept and Adherence

In a 2003 report,⁹⁸¹ the World Health Organization (WHO) defined adherence as “the extent to which a person's behaviour—taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider.” The primary reason for inadequate HT control seems to be nonadherence with long-term treatments, both for lifestyle changes (LSCs) and for taking the medications prescribed. In 2012, in a new WHO report, the authors differentiate the processes involved, such as adherence to medication and adherence management.⁹⁸² According to the those guidelines, adherence to medication is made of three major components: initiation, implementation, and discontinuation. Initiation is the time from prescription to taking the first dose of the medication; implementation corresponds to the coincidence between dose taken by the patient and dose prescribed; and discontinuation indicates the break in the process, when the next dose to be taken is skipped and the treatment is later interrupted.⁹⁸²

Though there are various synonyms for adherence, such as compliance, conformity and capacitance, the proper term for HT treatment is still “adherence.” Adherence issues are

often hard to detect and even harder to quantify. To improve HT control, it is important to combine efforts in order to identify patients who are not adhering to their treatment. Dropout rates are high in the first months of treatment, and patients may also not follow their prescription when taking medications. This situation has been described in medical literature since the 1970s⁹⁸³ and is still found in more recent reports.^{984,985} Lack of adherence to treatment is frequently defined as hypertensive patients taking less than 80% of prescribed medications. However, the spectrum of nonadherence from zero to over a 100% for those who take more than prescribed, which is also considered nonadherence to treatment.

17.3. Treatment Adherence Assessment Methods

There are many ways of measuring adherence to antihypertensive pharmacological treatment in clinical practice and in research, divided into direct methods, in which there is objective proof the patient has taken the medication, and indirect methods, where various strategies estimate whether the prescribed medication has or has not been taken. Choice of methods depends on for what purpose the information obtained will be used, the resources available for assessment, acceptance, how convenient the method is for the patient, and the costs involved.⁹⁸⁶ Measuring adherence is a complex task. There is no single gold standard method capable of encompassing the various facets of the process.³⁴⁴

The WHO suggests combining an indirect method and a direct one to measure adherence⁹⁸⁴ for chronic illnesses. In HT, indirect methods wind up the most widely utilized, since direct methods still lack validation, are more expensive, and are only available in research environments.

Structured self-reported scales are widely used in clinical research, such as the Morisky-Green Medication Adherence Scale. The Eight-Item Morisky Medication Adherence Scale⁹⁸⁷ evolved from a previous four-item scale,⁹⁸⁸ is more reliable ($\alpha = 0,83$ versus $\alpha = 0,61$) and has been validated for Brazilian Portuguese.⁹⁸⁹ The total score is classified as follows: 8 points mean high adherence; 6-7, medium adherence; below 6,

low adherence. Another instrument is the three-question Qualiaids Medication Adherence Questionnaire (QAM-Q), created by Brazilian authors. In terms of accurately detecting nonadherence, QAM-Q has 62.5% sensitivity and 85.7% specificity, 74.1% area under the ROC curve, and 90.9% positive predictive value.⁹⁹⁰

A review article on the subject of adherence and HT highlights the importance of increasing the availability and accessibility of more accurate measures to assess adherence. It also stresses that this is the main reason recent guidelines have emphasized the need to discuss medication adherence as a key issue in treating HT.⁹⁹¹ Chart 17.1 clarifies the advantages and disadvantages of several pharmacological treatment adherence assessment methods.⁹⁹²

17.4 Factors Interfering in Adherence to Treatment

Adherence to treatment is a complex, multidimensional process, with barriers divided into five different dimensions (Chart 17.2)^{985,993-996} that provide health care professionals with a more comprehensive perspective and enable to development of more effective interventions to improve BP control. Factors such as age, income, schooling and ethnicity/race play a major role in low socioeconomic status areas. The local health system and the nature of the health care staff may also influence adherence by hypertensive patients. In terms of disease and treatment, the most relevant factors are the chronic nature of HT and the absence of symptoms, the lifelong nature of the treatment and the complex drug regimen involved in some cases, and the undesirable side effects and drug interactions. Patient-related factors include disengagement with one's health issues and forgetting to take the medication.

17.5. Strategies to promote adherence to antihypertensive treatment

The main consequence of lack of adherence to treatment is the lack of HT control and, therefore, increased end-organ damage (EOD) and cardiovascular (CV) morbidity and mortality. These, in turn, have major economic impact, in consequence of greater health care spending and early retirement. Therefore, adopting strategies to promote better adherence to antihypertensive treatment, either in isolation or in combination, as summarized in Chart 17.3, intends to change that scenario.^{197,997-1006}

The strategies with the best evidence available and which could be more feasibly implemented in Brazil include:

- Self-measured BP (Level of Recommendation I/Level of Evidence B);
- More convenient dosing regimens: lower possible doses, single daily dose, combination of antihypertensives in a single pill (Level of Recommendation I/Level of Evidence A);
- Deploying multidisciplinary teams to care for hypertensive patients, including physicians, nurses, pharmacists, physical educators, physical therapists, nutritionists, psychologists, social workers, and community health workers (Level of Recommendation I/Level of Evidence B).

17.6. Conclusion

Optimizing antihypertensive treatment adherence indices contributes to lower morbidity, mortality, and health care costs. Current therapeutic options include both pharmacological and nonpharmacological treatment regimens with proven effectiveness. Adherence to treatment plans and consequent hypertension control is still a major challenge in health care. Thus, combining efforts to met the actual needs of hypertensives has become the primary objective in the work of changing the current hypertension scenario.^{18.} Perspectivas

Key Takeaways

HT control rates in Brazil are still unsatisfactory. There are many reasons for the lack of hypertension control, but one of the most important is the lack of adherence to treatment.

Adherence to treatment is a complex, multidimensional process, where we can identify barriers connected to sociodemographic conditions, pharmacological treatment, health care systems, patients, and the disease itself.

Adherence issues are often hard to detect and even harder to quantify.

Measuring adherence is a complex task. There is no single gold standard method capable of encompassing the various facets of the process.

The strategies with the best evidence available and which could be more feasibly implemented in Brazil are:

- Self-measured blood pressure (LR: I, LE: B);
- More convenient dosing regimens: lower possible doses, single daily dose, combination of antihypertensives in a single pill (LR I/LE A);
- Deploying multidisciplinary teams to care for hypertensive patients, including physicians, nurses, pharmacists, physical educators, physical therapists, nutritionists, psychologists, music therapists, social workers, and community health workers (LR I/LE B).

Chart 17.1 – Advantages and disadvantages of several pharmacological treatment adherence assessment methods

METHODS	ADVANTAGES	DISADVANTAGES
DIRECT METHODS		
Blood or urine testing	Objective and allows concentration of medication to be determined.	High cost. May be affected by biological factors and by “white-coat adherence”*
Adding markers	Objective and may be use in placebos in clinical research.	Requires high-cost quantitative assays and collection of body fluid samples.
Supervised administrations	Accurate.	Patients may hide pills under their tongue and discard them afterwards. Hard to deploy in outpatient settings for hypertensive patients, may be reserved for cases of resistant and refractory hypertension.
INDIRECT METHODS		
Structured adherence surveys (self-reported scales)	Simple, easy, cheap, and widely used.	Subject to error as interval between visits increases. Results may be distorted by patients.
Physician's impression	Easy and cheap.	Low sensitivity.
Manual pill count	Objective, quantifiable, and easy to execute.	Requires patient collaboration in returning the medication. Data may be altered by individuals.
Refilling prescriptions	Objective and easy data collection.	Requires computer applications and centralized pharmacies and record-keeping.
Clinical response	Simple and easy to perform.	Other factors may impact clinical response in addition to adherence.
Electronic devices	Accurate and identifies standards in measurements. Results are easily quantifiable.	High-cost method, requiring repeat appointments and processing data outputs.

* “White-coat adherence”: situation where patients have higher adherence to recommended treatments before medical appointments or collection of samples for laboratory tests.

Chart 17.2 – Factors interfering with adherence to antihypertensive treatment**SOCIODEMOGRAPHIC FACTORS**

- Sex;
- Age;
- Low educational level;
- Low income;
- Racial/ethnic minorities;
- Access to transportation, distance and living in rural areas;
- Pandemics and disaster conditions.

FACTORS RELATED TO PHARMACOLOGICAL TREATMENT

- Lack of medications at health care centers;
- Cost of purchasing medications;
- Adverse effects;
- Complex dosing regimens;
- Improper therapy regimen;
- Continuous and prolonged treatment.

FACTORS RELATED TO HEALTH CARE SYSTEM AND STAFF

- Inadequate doctor/patient relationship;
- Absence of multidisciplinary team;
- Lack of individualized treatment;
- Failure to identify nonadherence;
- Ineffective communication;
- Overloaded health care staff;
- Outdatedness.

PATIENT-RELATED FACTORS

- Denial of diagnosis;
- Poor perception of treatment benefits;
- Inadequate knowledge about the disease and the treatment;
- Forgetting to take the medication;
- Low motivation and self-esteem;
- Fear of addiction and of adverse effects of medications.

DISEASE-RELATED FACTORS

- Absence of symptoms;
- Long-term complications;
- Presence of other associated comorbidities;
- Alcohol and drug abuse;
- Impact on quality of life.

Chart 17.3 – Strategies to promote adherence to antihypertensive treatment**PATIENT INTERVENTIONS**

- Motivational strategies;
- Home blood pressure monitoring (measuring BP at home);
- Distance telemonitoring services;
- Health education to promote self-care;
- Use of pill dispensers and reminders;
- Encourage social and family support;
- Group education sessions;
- Text messaging.

INTERVENTIONS IN PHARMACOLOGICAL TREATMENT

- Avoid high doses in monotherapy;
- Choosing medications with lower adverse events profile;
- More convenient dosing regimens;
 - ✓ Single daily dose;
 - ✓ Two to three antihypertensives combined in a single pill;
- Easy-to-understand prescriptions (handwritten or print);
- Adjusting treatment for the patient's clinical and demographic characteristics (POC, older adults, women, the obese, diabetic patients).

HEALTH CARE SYSTEM AND STAFF INTERVENTIONS

- Bonding with patients (having a fixed health care team);
- Clear communication;
- Calling patients who miss their appointments;
- Home visits;
- Having multidisciplinary teams (physicians, nurses, pharmacists, physical educators, nutritionists, psychologists, social workers, community health workers);
- Facilitate access to medications.

18. Perspectives

18.1. Introduction

The goal of this chapter is to discuss, based on evolving scientific knowledge about hypertension in the last few decades and more recent evidence, the possible advances and adjustments that will impact daily clinical practices and the challenges involved in diagnosis, treatment, and follow-up for hypertensive patients. It should be stressed that, unlike the previous chapters, where recommendations were rigorously classified by level of scientific evidence and level of recommendation, this section was designed to introduce possible rational vistas, based on the knowledge we have acquired thus far for this complex, multifactorial disease, with cardiovascular (CV), cerebral, and renal consequences that heavily determine morbidity and mortality, to the point that it has become the leading cause of death throughout the world.

18.2. Definition, Epidemiology, and Primary Prevention

With the gradual rise in life expectancy in both developed and developing countries, prevalence rates for hypertension (HT) are likely to increase even more. On average, there was a 1.4-year gain per decade of life in developed countries and a 1.2-year gain in Latin American countries from 1980 to 2011.¹⁰⁰⁷ It is widely known that, as we grow older, blood pressure levels increase, and from age 60 onward, systolic blood pressure (SBP) increases while diastolic blood pressure (DBP) decreases. This leads to higher pulse pressure (PP). These are important aspects when assessing risk factors and treatment strategies (Figure 18.1).^{180,1008}

18.3. Blood Pressure and Vascular Damage

The increase in CV risk starting at SBP = 115 mm Hg and DBP = 75 mm Hg is well-known,⁷⁸ and BP measures remain the diagnostic marker of hypertensive disease. However, science is still trying to better understand biomarkers capable of early identification of vascular damage in hypertensive disease, even before the onset of higher BP values, as well as to develop their clinical applicability. The goal is to increase the accuracy of CV risk stratification in low- to moderate-risk individuals.^{82,139,1010}

Central systolic blood pressure assessments and arterial stiffness assessed by pulse wave velocity (PWV) are based on robust evidence with the goal of early identification of vascular damage and the ability to identify and re-stratify individuals initially classified as having low to moderate risk but who could actually be at high risk. In addition, PWV values above 10 m/s may indicate the presence of subclinical end-organ damage,^{156,298,1011} and increased central systolic BP is a predictor of the development of hypertension.¹⁰¹² Another way of assessing vascular damage is the ability to identify lost or impaired endothelial function, as well as to understand its pathophysiology, which includes genetic predisposition and chronological aging, as well as changes in inflammatory and immune activity, insulin sensitivity, and cholesterol-rich lipoproteins.^{112,114}

Currently, the method most widely used to analyze in vivo endothelial function is flow-mediated dilation (FMD), but it remains restricted to research settings.¹¹⁸ It is possible that, with new evidence in hypertensive and cardiovascular disease, the method will become more reliable and safe for use in clinical practice, further enhancing the early identification of vascular damage.^{1013,1014}

18.4. Cardiac Biomarkers

Though there has been great progress in the search for markers to estimate arterial damage, we cannot underestimate older tests that identify CV risk, such as electrocardiogram (ECG), magnetic resonance or, more recently, coronary calcium score, among others, for diagnosis of left ventricular hypertrophy (LVH).^{1015,1016} There is robust evidence in favor of using B-type natriuretic peptides and N-terminal pro-B-type natriuretic peptides (NT-proBNP) as well as high-sensitivity Troponin T (hs-TnT), in risk stratification for fatal or nonfatal CV events and all-cause mortality. B-type natriuretic peptides are secreted by myocytes as counterregulatory response to pressure or volume overload of the myocardial wall, to increased sympathetic tone and to vasoconstriction, but also integrate CV stress and hemodynamic from multiple sources.¹⁰¹⁷ Cardiac troponins are structural proteins in the contractile mechanism of heart muscle cells, secreted into circulation after cell damage.¹⁰¹⁸

A recent study found that simply raising NT-proBNP and/or hs-TnT in prehypertensive patients enabled the identification of approximately 1/3 of those that who would later have CV outcomes or be admitted for heart failure (HF) within 10 years, individuals who could potentially benefit from pharmacological treatment.¹⁰¹⁹ It has also been shown that NT-proBNP can estimate all-cause mortality and nonfatal CV outcomes for high-risk hypertensive diabetes patients in 2.6 years with the same predictive power as the whole set of the 20 most significant clinical and laboratory variables use most frequently, such as hs-TnT, age, albumin, history of HF, heart rate, history of stroke, HbA1c, smoking, LVH in ECG, ECG Q-waves, history of atrial fibrillation, any branch block in ECG, urine albumin/creatinine ratio, SBP, sex, history of coronary artery disease, low-density lipoprotein cholesterol, estimated glomerular filtration rate, insulin use, and DBP.¹⁰²⁰

18.5. Diagnosis and Classification

HT diagnosis, based on in-office measurement results and using proper techniques and devices, is defined as SBP $\geq$ 140 mm Hg and DBP $\geq$ 90 mm Hg.¹⁶⁴ The latest international guidelines recommend that HT diagnosis, whenever possible, be based on in-office blood pressure measurements, preferably unattended, or else by out-of-office measurements (ABPM and HBPM). In addition, there is a debate whether reference values to establish HT should be even lower or not.^{37,164,186,1021}

It seems clear that identifying HT, whether treated or untreated, by phenotype allows for risk stratification and for the definition of more individualized treatment strategies.^{180,212} Another interesting topic is the use of self-measured blood pressure (SMBP) as a method for increasing patient engagement with their own illness and improving adherence to treatment,

in addition to providing health care professionals with more information about the patient's everyday BP levels.¹⁰²²

The COVID-19 pandemic means acknowledging the global development of telemedicine techniques is critical. Apparently, distance monitoring through digital platforms and mobile applications for hypertensive patients has come to stay, facilitating conversations between health care teams and patients and the consequent information exchange and beneficial adjustments to lifestyle changes and even to treatment itself, with more focus on prevention and improving disease control. However, digital technology may further expand the scope of hypertension, following the lead of diabetes mellitus, enabling the development of increasingly accurate, continuous cuff-less blood pressure monitoring devices, syncing up with the smartphones that are now within reach for most of the population.^{388,1023,1024}

Finally, it is possible that in coming years, more attention given to patients with SBP $\geq$ 130 mm Hg and DBP $\geq$ 85 mm Hg (now classified as prehypertensive in these and in other guidelines) will change our understanding of HT diagnoses.¹⁰²⁵

18.6. Complementary Assessment and Cardiovascular Risk Stratification

The use of biomarkers for early identification of subclinical injuries, as well as higher CV risk, even at the early stages of high BP, brings with it the expectation that, for specific indications, individuals could and should receive early care for their conditions.¹³⁹ There are also biomarkers for vascular damage. For some, like the ankle-brachial index (ABI), calcium score and PWV,^{298,1011} there is evidence in favor of the previous statements, though they are not widely available in clinical practice. Meanwhile, others, such as FMD, are still restricted to research settings.¹¹⁸ Furthermore, researchers are currently working on a set of substances associated with inflammation that may ultimately be closely connected to endothelial dysfunction and to atherosclerosis, but which still require more robust evidence before they can be used in clinical practice.^{180,271,1014,1022,1026}

In terms of CV risk stratification, the progressive integration of biomarkers will allow us to more accurately establish the true risk level for each individual, especially for intermediate-risk hypertensive patients. Approaches of this sort offer the possibility of a more personalized medicine, with greater assertiveness in decisions connected to classification and treatment.^{156,298,1011}

In addition, in the field of precision medicine, usually based on genomics and metabolomics, there are already validated clinical scores capable of identifying patients at higher risk of early hypertension, as well as reference values for some of those biomarkers for the Brazilian population, adjusted for sex and age. The possibility of less sophisticated markers certainly works towards the improvements in accuracy we want to provide indications for specific assessments in clinically preselected patients, as is already usually the case in the investigation of secondary HT in the presence of clinical signs and positive screening tests.^{158,159}

18.7. Goals and Treatment

Following the scientific advancements and proofs discussed in the previous sections, it is reasonable to imagine that, in particular situations, early treatment onset and the pursuit of lower BP control targets may be indicated to prevent outcomes associated with increased BP and to minimize the so-called residual risk.^{307,1027} In addition, the pharmacological treatment strategy based on two- or even three-drug combinations (at low doses), even at the early stages of the disease, should become increasingly prominent in guideline recommendations, while monotherapy may become an important strategy for individuals now classified as high-risk prehypertensives or those with changes in biomarkers (Figure 18.2).^{307,1023,1028,1029}

It is possible that in the world of hypertension, according to current studies, our goal may be to control central and peripheral BP parameters, as long as that strategy can prove its ability to maximize reductions in major CV and renal outcomes.^{1030,1031} Finally, though the prospect seems far-off, there is a real possibility that highly specific molecular tools will be available for HT treatment, such as RNA-mediated interference, which is simply post transcription gene silencing (PTGS) of overexpression of the protein of interest.^{388,1032} Gene therapy for HT seems promising and has led to proven results in experimental studies involving the target-gene encoding the hepatic angiotensinogen. However, there is a known path for its clinical application after it is proven to be selective, effective and, above all, safe. Though many important perspectives are on the table, apparently the greatest challenge of all, in Brazil and worldwide, is much simpler. Its goals include improving diagnosis, adequate treatment, teamwork, and better blood pressure control in order to achieve significant reductions in renal and cardiovascular morbidity and mortality.

Guidelines

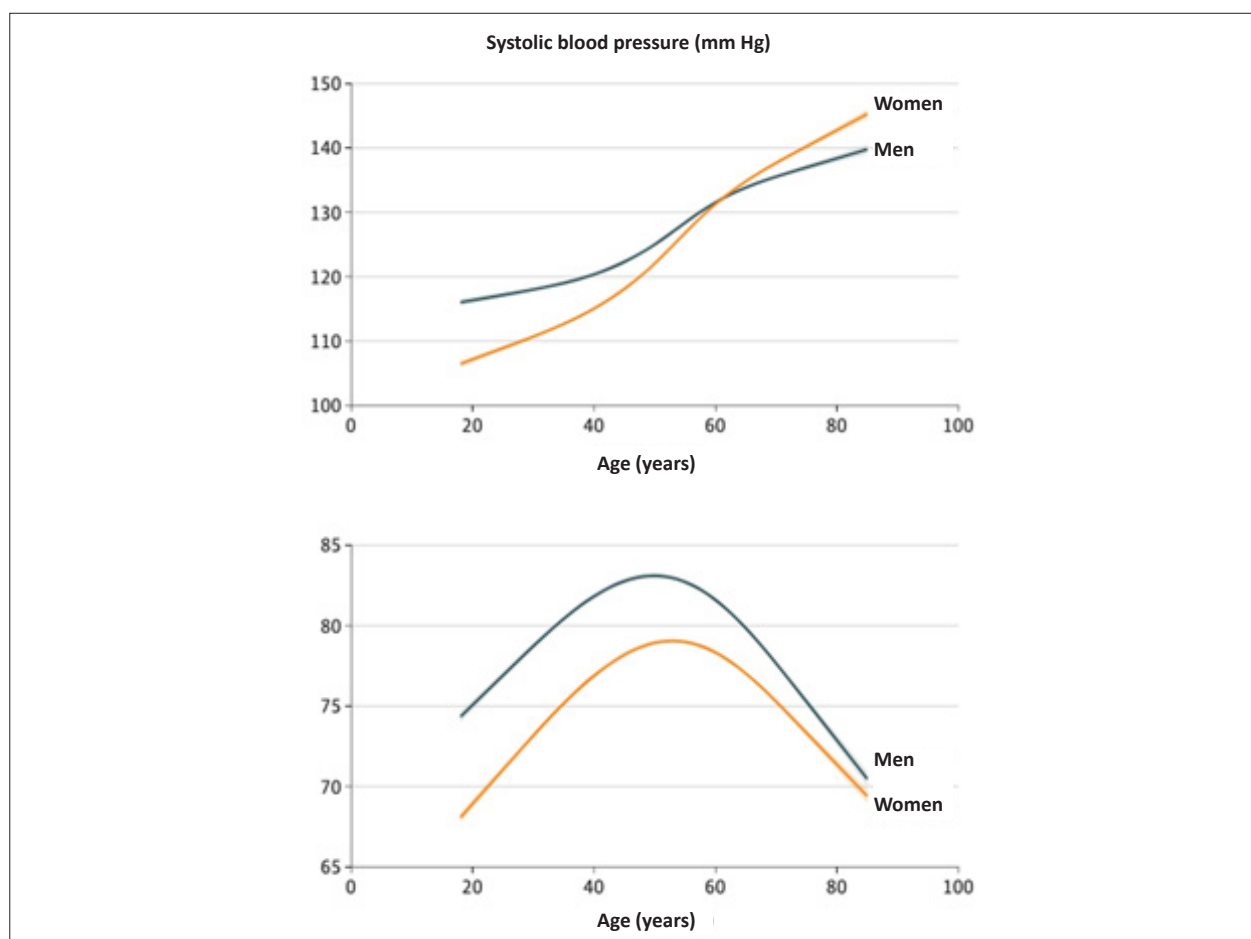


Figure 18.1 – Systolic and diastolic blood pressure behavior throughout life and by sex.
Source: Ji H et al., 2020.¹⁰⁰⁸

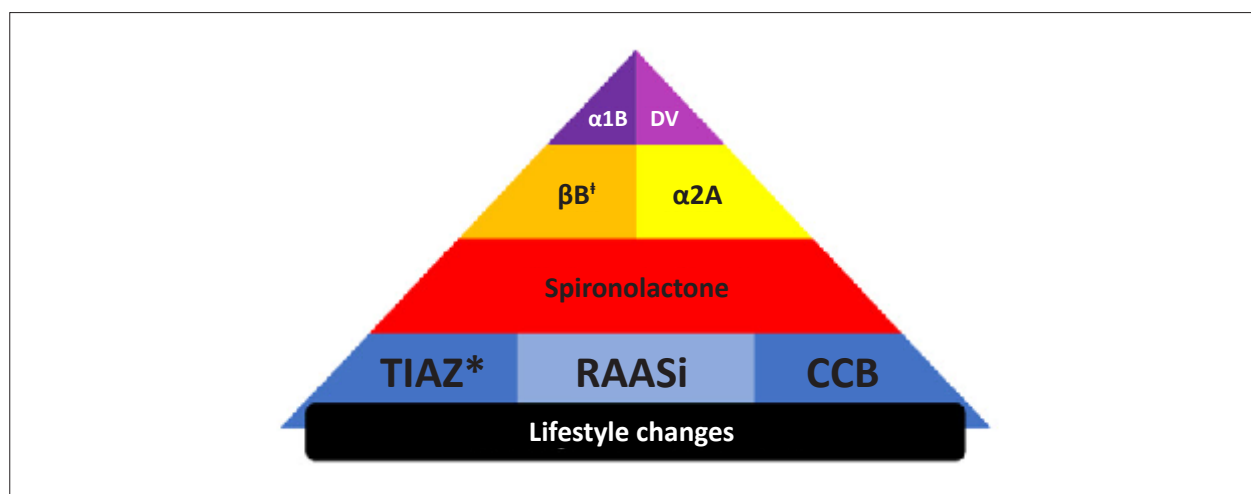


Figure 18.2 – Drug octet for hypertension treatment.
Source: Feitosa et al., 2020.¹⁰²⁸ $\alpha 1B$: alpha-1-adrenergic antagonist; $\alpha 2A$: central alpha-2 agonist; BB: beta-blocker; BB, may be indicated before specific clinical conditions; CCB: dihydropyridine calcium channel blocker; DV: direct-acting vasodilator; RAASI: renin-angiotensin-aldosterone system inhibitor; TIAZ*: long-acting thiazide or thiazide-like diuretic up to 30 mL/minute of estimated glomerular filtration rate and in the absence of hypervolemia, else switch to loop diuretic.

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Guidelines



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Statement

Position Statement on Indications and the Safe Reintroduction of Cardiovascular Imaging Methods in the COVID-19 Scenario – 2021

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Note: These statements are for information purposes and should not replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

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Declaration of potential conflict of interests of authors/collaborators of the Position Statement on Indications and the Safe Reintroduction of Cardiovascular Imaging Methods in the COVID-19 Scenario – 2021

If, within the last 3 years, the author/collaborator of the statement:

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Content

Cover Letter	662
1. Introduction	662
2. Safety Protocols for the Reintroduction of Cardiovascular Imaging Examinations in the COVID-19 Era	663
2.1. Infrastructure and Safety Policies	663
2.2. Prioritizing Indications and Choosing the Cardiovascular Imaging Method	664
2.3. Personnel Protection	664
2.4. Equipment Maintenance	664
2.5. Special Precautions for Stress Tests	664
2.6. Special Precautions for TEE	666
2.7. Special Precautions for Pediatric Echocardiography	666
2.8. Special Precautions for Fetal Echocardiography	666
3. Echocardiography in Adult Patients in the COVID-19 Era	666
3.1. Prioritization and Indications for Transthoracic Echocardiography in Adult Patients at Low Risk For COVID-19	666
3.1.1. High-priority Examinations (Essential Procedures)	666
3.1.2. Medium-priority Examinations	667
3.1.3. Low-priority Examinations	667
3.2. Prioritization and Indications for Transthoracic Echocardiography in Adult Patients with Suspected or Confirmed COVID-19	667
3.3. Protocols for Transthoracic Echocardiography in Adult Patients in the COVID-19 Era	667
3.3.1. Focused Echocardiography	667
3.3.2. Focused Ultrasound – Indications, Protocols, and Main Findings	668
3.3.3. Focused Lung and Pleural Ultrasonography	668
3.3.4. Focused Cardiovascular Ultrasound	669
3.4. Prioritization and Indications for Stress Echocardiography in the COVID-19 Era	670
3.5. Prioritization and Indications for Transesophageal Echocardiography in Adult Patients in the COVID-19 Era	670
4. Pediatric, Congenital, and Fetal Echocardiography in the COVID-19 Era	671
4.1. Prioritization and Indications for Transthoracic Echocardiography in Pediatric and Congenital Patients	671
4.2. Optimization of the Transthoracic Echocardiography Protocol in Pediatric and Congenital Patients	671
4.3. Prioritization and Indications for Fetal Echocardiography	672
4.4. Prioritization and Indications for Transesophageal Echocardiography in Pediatric Patients	672
4.5. Protocol for Transesophageal Echocardiography in Pediatric Patients	672
5. Vascular Ultrasonography in the COVID-19 Era	672
5.1. Prioritization and Indications for Vascular Ultrasonography in Patients at Low Risk for COVID-19	672
5.2. Prioritization and Indications of Vascular Ultrasonography in Patients with COVID-19	673
5.3. Situations Where Vascular Ultrasonography is Not Recommended for Patients with COVID-19	673
5.4. Optimization of Vascular Ultrasonography Protocols	673
6. Cardiac Magnetic Resonance in the COVID-19 Era	673
6.1. Prioritization and Indications	673
6.2. Optimizing Cardiac Magnetic Resonance Protocols	673
7. Cardiovascular Computed Tomography in the COVID-19 Era	674
7.1. Prioritization and Indications	674
8. Nuclear Cardiology in the COVID-19 Era	674

8.1. Prioritization and Indications	674
8.2. Ventilation/Perfusion Scintigraphy	674
9. Conclusion	675
References	676

Cover Letter

The objective of this position statement is to inform clinicians, cardiologists, and medical imaging specialists on the recommended procedures, flows, and protocols for the duration of the SARS-CoV-2 pandemic aiming at a more efficient protection of health care professionals and patients. Recommendations are based on the best available scientific evidence at the moment and on the consensus among experienced specialists. Since the first case of the new coronavirus disease (COVID-19) in Brazil, many changes in recommendations and a large scientific debate regarding some of them have occurred within various sources of scientific knowledge. This is due to our currently incomplete knowledge on COVID-19, including its pathophysiological processes and aspects of SARS-CoV-2 transmission. Another reason for a variability in recommendations is related to the epidemiological phase of the pandemic in each region of the country. Notably, in a country with continental dimensions such as Brazil, the pandemic can reach different transmission phases in a specific moment, thus requiring particular measures for each region and phase of the pandemic.

In the beginning of the pandemic, a phase of great attention and lack of knowledge on what the future held, the Cardiovascular Imaging Department (DIC) of the Brazilian Society of Cardiology (SBC) published a brief and essential version of a position statement. The document provided rapid and practical fundamental guidance regarding safety procedures during non-invasive cardiovascular imaging procedures. This document was absolutely essential at that moment for providing the best possible protection for health care professionals. After the publication of a summary document in the initial stage of the pandemic, DIC-SBC and its specialists have deemed timely to update that position statement (now published in the form of an official scientific publication); this should include not only a much wider view of the procedures in light of the data acquired since then, but also a customized orientation for each epidemiological phase of the pandemic that could be useful for professionals working in non-invasive cardiovascular imaging for the next months or possibly years of coexisting with COVID-19.

1. Introduction

In view of the new coronavirus disease (COVID-19) pandemic and its high transmissibility, an urgent reorganization of cardiovascular imaging services was necessary for minimizing exposure to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and ensure the protection of patients, physicians, and personnel without compromising patient assistance. It was recommended that elective outpatient examinations be deferred (when deemed non-essential) for reducing exposure and risk of cross-contamination, and that personal protective equipment (PPE)

Statement

be rationally used.¹⁻³ The use of PPE became mandatory for all personnel in the workplace, including reception workers, nursing technicians, nurses, technologists, biomedical scientists, and doctors. All patients were instructed to use masks. Specialists discussed, along with the requesting doctors, the actual need for test urgency and the most suitable cardiovascular imaging modality for each specific clinical situation. On the other hand, it is known that: (a) Cardiovascular imaging is frequently necessary for primary prevention, clinical management, and differential diagnosis in many situations, and chronically postponing it can be harmful; (b) COVID-19 can cause severe cardiovascular manifestations, especially in vulnerable individuals such as older people, immunosuppressed patients, or those with previous cardiovascular disease and/or cardiovascular risk factors (hypertension, diabetes, obesity);⁴⁻⁶ (c) when the lungs are severely affected by COVID-19, the cardiac function can suffer greater impact, especially in the right ventricle. In a moment when the number of COVID-19 cases present a relative decrease, health care services will be able to progressively increase their working hours according to the pandemic tendency and guidance provided by local public authorities. Nevertheless, the reintroduction of cardiovascular imaging examinations should follow various safety protocols, as described in the next section.

2. Safety Protocols for the Reintroduction of Cardiovascular Imaging Examinations in the COVID-19 Era

Outpatient scheduling should be progressive and consider indications for appropriate use,^{2,7} the indication priority, risk of COVID-19, and the phase of the pandemic. Areas going through the peak transmission phase should prioritize essential examinations (high-priority cases), that is, where the results are expected to bring clinical benefits or a change in management.^{1,8} Medium-priority indications are those where examinations, although elective or in asymptomatic patients, can contribute to the implementation of primary or secondary prevention measures, in the adjustment of

currently used medications, or in medium-term changes in management, potentially impacting the clinical outcome. Low-priority indications are those where tests could be deferred until after the peak of the pandemic and be gradually reintroduced once the number of cases is reduced.

Imaging examinations of patients with COVID-19, especially in outpatient settings, should be deferred (when possible) until the patient reaches the criteria for cure. At the moment of elaboration of this position statement, the Centers for Disease Control and Prevention (CDC) considers 2 criteria for releasing patients from isolation after COVID-19: The “symptom-based strategy” states that patients should be released from isolation 10 days after symptom onset; the “time-based strategy” considers that patients should be released 10 days after the first positive test (RT-PCR SARS-CoV-2).⁹ These criteria can be adjusted according to orientations of the local infection committee. If the cardiovascular examination is considered essential, it should be directed to the clinical question (focused) but sufficiently complete to avoid repetition, and follow all recommendations regarding protective measures. In addition, redundant or rarely appropriate examinations can generate an additional financial impact to that caused by the pandemic. These recommendations on indications and prioritization are valid as long as the pandemic persists and are summarized in Table 1.

Defining “who,” “when,” and “how” cardiovascular imaging examinations should be used is fundamental for reducing contamination risks for the patients and health care professionals while ensuring high-quality assistance. These measures are described below.

2.1. Infrastructure and Safety Policies

- A triage questionnaire for defining COVID-19 risk should be applied when scheduling an appointment, at confirmation, and on the day of the examination (respiratory symptoms and contact with confirmed COVID-19 case). At admission, temperature checks should also be performed. The same triage protocol should be applied to the staff.

Table 1 – Indication prioritization for rescheduling cardiovascular imaging examinations according to the phase of the pandemic and COVID-19 risk

Level of priority	Prioritization rationale
High priority (Consider performing the examination in the next hours or the next 2 to 4 weeks)	• Acute cardiovascular symptoms or with recent worsening • Evaluation before urgent clinical therapy • Planning of urgent cardiovascular interventions • Safety monitoring of clinical therapy • Monitoring after recent invasive or surgical therapy To be performed regardless of the pandemic phase
Medium priority	• Progression monitoring of chronic myocardial disease or asymptomatic severe chronic valvular disease • Clinical therapies requiring monitoring • Monitoring of therapy results • Initial assessment of a new and unexplained heart murmur, even if asymptomatic Defer until the deceleration phase of the pandemic, preferably for patients at low risk for COVID-19
Low priority	• Routine evaluation of chronic disease in individuals not eligible for clinical, surgical, or invasive therapy Defer until the control phase of the pandemic for patients at low risk for COVID-19

Adapted from the recommendations of the American Society of Echocardiography.¹⁰

- Instructions regarding social distancing, mask use, and hand hygiene should be provided when scheduling an appointment and reinforced at admission.
- Telemedicine applications should be implemented.
- Visual displays containing information on protective measures should be placed on waiting rooms and strategic places (in more than one language).
- Hand sanitizer should be widely available.
- Patients should be instructed to arrive on time or to wait for their turn inside the car; the number of accompanying persons should be limited.
- The number of seats in the waiting room should be reduced so as to guarantee social distancing.
- Acrylic glass barriers or distancing cones should separate patients and the reception staff.
- The time between examinations should be extended for avoiding crowded rooms and allowing proper cleaning. Facilities should consider opening at non-business hours or weekends.
- Equipment and surface cleaning protocols should be performed after each examination according to the local infection control policies and the type of examination.
- Communication with patients or financial transactions should be preferably performed online.
- There should be 2 patient flows: One for patients with suspected or confirmed COVID-19 and another for patients without the disease. Rooms, equipment, and circulation areas should be separated for the 2 groups.
- Ideally, rooms should be well-ventilated and have negative pressure when performing procedures that generate aerosols (transesophageal echocardiography [TEE], exercise stress tests).
- PPE stocks should be continuously monitored and maintained.
- Contaminated material should be disposed of according to health surveillance agency guidelines.

2.2. Prioritizing Indications and Choosing the Cardiovascular Imaging Method

- Define the priority level of the examination (according to the local phase of the pandemic and the risk of COVID-19 [Table 1]).
- Select the best test for providing essential information on the patient's clinical condition.
- Consider replacing an examination for another with similar accuracy, but lower risk of COVID-19.
- Avoid performing multiple tests or inappropriately repeating the same examination.

2.3. Personnel Protection

- Practice frequent hand hygiene and constant mask use.
- Appropriately use PPE according to the required protection level (for droplets or aerosols). Table 2 summarizes the use of PPE according to the protection

level required by each type of examination, the risk of COVID-19, and location.

- Participate in frequent institutional training on donning and doffing PPE, its duration of use and storage, as well as hand hygiene. Evidence shows that the highest chances of infection in professional settings occur at the moment of inadequate PPE removal. Steps and guidance for donning and doffing PPE are demonstrated in Figures 1 and 2.
- Limit the number of professionals in the examination and report rooms.
- In case of examinations that require close contact between the professional and the patient, such as echocardiography and vascular ultrasonography, consider the use of a plastic or acrylic glass barrier.
- Limit test duration by using more objective or focused protocols. In case of patients admitted with suspected or active COVID-19, ultrasound/echocardiography examinations should be performed at the bedside, without electrocardiographic monitoring. Images should be obtained first and measurements should be performed only after the professional leaves the room and the equipment is disinfected.
- If possible, concentrate appointments of patients with suspected or confirmed COVID-19 within a specific time frame for minimizing exposure and rationalizing the use of PPE.

2.4. Equipment Maintenance

- Restrict the PPE components to those minimally necessary for performing the examination in order to reduce the need for cleaning and disinfection after the procedure, as well as the risk of contamination and cross-transmission.
- Consider the use of a protective cover for the equipment and transducer (in case of ultrasound equipment), as long as it does not hinder equipment use or prolong test duration.
- All equipment and accessories should be cleaned and disinfected after each use according to equipment disinfection guidelines. Stress tests and TEE, or examinations performed on patients with aerosol emission (in the intensive care unit [ICU], on invasive or non-invasive ventilation) require longer appointments, since disinfection should be prolonged. Cleaning and disinfection protocols are detailed on Supplementary Material.

2.5. Special Precautions for Stress Tests

Stress tests are essential in the evaluation of patients with suspected or confirmed coronary heart disease. They include exercise or pharmacological stress tests with any of the nuclear cardiology imaging modalities (single-photon emission computed tomography/positron emission tomography [SPECT/PET]), echocardiography, or cardiovascular magnetic resonance imaging (CMR). However, stress tests can increase the risk of contamination by droplets and should be deferred (for patients at low risk for COVID-19) or cancelled (for patients with suspected or confirmed COVID-19). Pharmacological stress should have preference over exercise. Once the pandemic fades, when clinically appropriate, exercise stress tests should include additional precautions, such as:¹

Statement

Table 2 – Use of personal protective equipment during cardiovascular imaging examinations in the COVID-19 era according to exposure risks

	TTE, CCT/CMR, pharmacological stress test (Echo/SPECT/PET/CMR)	TEE, exercise stress test (Echo/SPECT/scintigraphy)
Low risk for COVID-19	Standard safety level Mandatory hand hygiene Surgical mask	Protection against aerosols:** Mandatory hand hygiene N-95/PFF2 respirator* Isolation gown (preferably waterproof) Examination gloves Surgical cap
Suspected or confirmed COVID-19 cases	Protection against droplets Mandatory hand hygiene N-95/PFF2 respirator* Isolation gown Head covering Examination gloves Safety goggles	Face shield; protection goggles when face shields not available Ideally, place patients with COVID-19 in negative pressure rooms Attempt to replace examination for an alternative method

* In case of complete unavailability of N-95 respirators or equivalents, wear a single-use surgical mask in addition to a face shield. ** Also applicable to all examinations performed with patients admitted in intensive care units (ICUs), on invasive or non-invasive ventilation. These recommendations should be followed by all personnel directly involved in the procedure (physicians, nursing technicians, technologists, etc.). CCT: cardiovascular computed tomography; CMR: cardiovascular magnetic resonance imaging; Echo: echocardiography; PET: positron emission tomography; SPECT: single-photon emission computed tomography; TEE: transesophageal echocardiography; TTE: transthoracic echocardiography.



Figure 1 – Sequence for donning personal protective equipment.



Figure 2 – Sequence for doffing personal protective equipment.

- Assess the facility's air circulation patterns – consult with the engineering department on optimized equipment/staff. Given the uncertainty regarding the aerosol generating capacity of a stress test, an exclusive room should be used for exercise tests, if possible, with negative pressure.

- Avoid manual blood pressure measurement, if possible. Automatic blood pressure measurement is commonly used and reasonably precise both in stationary patients or those subjected to pharmacological stress.

- The supervising team should keep a distance (2 meters) from the patient, when possible.

- All staff involved in the test should wear a face shield (particularly during exercise stress echocardiography) and gloves, in addition to the PPE required for all examinations.

- When possible, the patient should be encouraged to wear a mask while exercising.

- If exercise is deemed necessary, consider testing for COVID-19 before the test.

- A careful choice of exercise protocol should be made since longer exercises increase the duration of patient-team interaction. The bicycle protocol is associated to lower levels of peak minute ventilation.

2.6. Special Precautions for TEE

Among all the echocardiography modalities, TEE is probably the one with the highest risk of health care team contamination due to the handling of the patient's airways, contact with fluids, close contact between the patient's mouth and the professional, and to the cough reflex that can happen during the probe passage towards the esophagus. Indications for this test should thus be carefully evaluated, and the highest precaution level is recommended (even for tests performed in the operating room or in patients that do not have suspected or confirmed COVID-19)^{2,3,8,12,13} (see Table 2). Ideally, TEE should be performed in an exclusive room containing protective covers for the echocardiography equipment (isolation or waterproof covering) and for all the necessary equipment, in addition to a strict and lengthy disinfection protocol for environmental surfaces between each test (approximately 1 hour).

2.7. Special Precautions for Pediatric Echocardiography

Considering that children have a higher possibility of being infected with COVID-19 and be asymptomatic or show minimum symptoms, the triage measures that apply to adult patients can be insufficient, requiring adjustments in outpatient or inpatient echocardiography. In case of an active and cooperative patient, the echocardiography physician should preferably be the only person in contact with the child. Children under 2 years old have difficulties wearing masks, which leads to a higher risk of exposure to the virus. In addition to the main form of transmission of SARS-CoV-2 (through respiratory droplets), transmission through fomites has been assumed plausible.¹⁴ Therefore, diaper changes should be avoided, if possible, during the examination and if necessary, performed with adequate hygiene. Due to the higher risk of an asymptomatic form of COVID-19 in children,

some facilities located in endemic regions choose to test new pediatric hospital admissions for SARS-CoV-2.

2.8. Special Precautions for Fetal Echocardiography

In facilities where fetal echocardiography (FE) is performed within the cardiology sector, pregnant women should be separated from pediatric patients, both in waiting and procedure rooms. Differently from previous viral outbreaks (H1N1, SARS-CoV, MERS-CoV), which were associated to severe complications in pregnant women, current information (although limited) suggests that these patients are not more susceptible to SARS-CoV-2 infections or, if infected, are not more prone to developing severe complications.¹⁵ However, given the uncertainty and possibility of an increase in risk as new data become available, the CDC alerts that pregnant women should protect themselves. Up to one accompanying person is allowed; for reducing exposure, the echocardiography room should ideally be occupied only by the pregnant patient and the examining physician.

3. Echocardiography in Adult Patients in the COVID-19 Era

Echocardiography is the first-line method in the diagnosis, prognostic evaluation, and therapeutic guidance of various cardiovascular diseases. During the new coronavirus outbreak, it remains a crucial imaging method, mainly due to its portability in comparison to other methods; this allows bedside examinations for isolated and/or critically ill patients.¹³ However, since it entails a close contact between the physician and the patient, echocardiography poses a high risk of infection by COVID-19.¹⁰

3.1. Prioritization and Indications for Transthoracic Echocardiography in Adult Patients at Low Risk for COVID-19

Even in patients at low risk for COVID-19, the reintroduction of outpatient examinations should be progressive, considering priority criteria and the phase of the pandemic (see Table 1).^{10,11,13} Next, we describe indications for each priority level.

3.1.1. High-priority Examinations (Essential Procedures)

- Individuals with acute cardiovascular symptoms or with recent worsening. Examples: New York Heart Association (NYHA) class III or IV heart failure, probable cardiac syncope, chest pain, arrhythmias, stroke, suspected acute valvular heart disease (mitral or aortic regurgitation), acute symptoms in patients with a prosthetic heart valve, or suspected symptomatic severe aortic stenosis with no previous diagnosis.⁷

- Evaluations before urgent clinical therapy, even in asymptomatic patients. Examples: baseline echocardiography prior to the initiation of chemotherapy or evaluation of left ventricle ejection fraction (LVEF) prior to implantation of a cardioverter defibrillator for primary prevention.

Statement

- Planning of urgent cardiovascular intervention: mitral valve repair, transcatheter aortic valve replacement (TAVR), left atrial appendage occlusion.

- Safety monitoring of clinical therapy. Example: chemotherapy follow-up in patients at high risk for cardiotoxicity, even if asymptomatic.

- Follow-up after recent invasive or surgical therapy. Example: suspected pericardial effusion after device implantation or heart surgery, even if asymptomatic.

- Suspected infective endocarditis with a high pre-test probability.

- Suspected pericardial disease or progression of pericardial effusion.

Indications for urgent (or high-priority) echocardiography in hospitalized patients are generally the same as before the pandemic (mechanical complications after acute myocardial infarction, tamponade, aortic dissection, and others).

3.1.2. Medium-priority Examinations

- Monitoring of the progression of chronic myocardial disease or asymptomatic severe chronic valvular disease. Examples: cardiomyopathy, aortic stenosis, primary mitral regurgitation, prosthetic valve dysfunction.

- New symptoms in patients with known heart or lung disease.

- Heart failure with reduced LVEF (HFrEF), when LVEF requires medical therapy or device implantation.

- Assessment before a routine procedure or therapy. Example: non-urgent surgery.

- Monitoring of therapy results. Example: treatment of regressing dilated cardiomyopathy or heart transplant rejection, Takotsubo syndrome (stress cardiomyopathy), Kawasaki disease, right ventricular (RV) dysfunction after pulmonary embolism (PE), pericardiocentesis, assessment of ventricular assistance device.

- Initial assessment of new unexplained heart murmur.

These examinations can be reintroduced in areas where the pandemic is waning.

3.1.3. Low-priority Examinations

These are elective examinations, requested annually or every two years for the follow-up of patients with asymptomatic chronic diseases or who have not shown changes in their health state, where the test result will not change treatment and/or short-term outcome. These examinations can be deferred to when virus transmission is reduced or restrictions are suspended or made flexible, especially if the patient has been subjected to echocardiography in the last 12 months.¹⁶

3.2. Prioritization and Indications for Transthoracic Echocardiography in Adult Patients with Suspected or Confirmed COVID-19

From a cardiovascular point of view, patients affected by SARS-CoV-2 can display evidence of myocardial dysfunction (both left and right), vascular alterations, arrhythmias, thromboembolic phenomena, and pericardial effusion.⁴

Therefore, echocardiography can also contribute to the clinical assessment of patients with COVID-19, in the following situations:^{2,3,17-20}

- Incapacitating dyspnea. Dyspnea is very common in patients with pneumonia secondary to COVID-19 (a situation where troponine levels are also increased, possibly leading to a false hypothesis of myocarditis). In this case, normal levels of B natriuretic peptide (BNP), even with elevated troponine, can exclude the need for echocardiography. Lung ultrasonography, in experienced hands, can help in the differential diagnosis between heart failure and pneumonia.

- Patients with previous heart disease with changes in hemodynamic state or signs and symptoms of disproportionate involvement of the lungs.

- Cardiomegaly on chest X-ray.

- Clinically significant arrhythmias or those with abrupt beginnings.

- Chest pain with electrocardiographic alterations and/or elevated troponin levels. In case of strong myocarditis suspicion and if CMR is indicated as crucial for the treatment, echocardiography can be initially omitted.

- Hemodynamic instability, respiratory failure, and/or shock of uncertain etiology.

- Suspected pulmonary hypertension and/or right ventricular dysfunction.

In difficult acoustic windows, the use of an echocardiographic contrast agent can be employed to ensure test results, reduce test duration, and avoid inadequate diagnosis or other unnecessary tests.^{21,22}

In patients with COVID-19, the examination should be focused on the clinical question. Serial echocardiography should be avoided unless there is clear change in the clinical state (hemodynamic instability). However, in the ICU, the echocardiogram is frequently used for monitoring the progression of critically ill patients, especially regarding fluid management. In this case, a focused ultrasound or focused echocardiography can be used. Protocols for these cases are described below.

3.3. Protocols for Transthoracic Echocardiography in Adult Patients in the COVID-19 Era

3.3.1. Focused Echocardiography

This examination is focused on the clinical question, but is sufficiently complete for including all clinical hypotheses. The protocol should be performed by echocardiographers in individuals with COVID-19 without electrocardiographic monitoring, and include the assessment of the following parameters:²

- Left ventricle: quantitative assessment of global systolic function (ejection fraction), signs of regional myocardial dysfunction, and cavity size.

- Right ventricle: assessment of global function, fractional area change (FAC) or tricuspid annular plane systolic excursion (TAPSE), cavity size, and tricuspid regurgitation velocity and pressure gradient, if possible.

Table 3 – Prioritization of CCT indications during the COVID-19 pandemic

	Low-priority indications	Medium-priority indications	High-priority indications (consider performing in the next hours or in up to 2 to 4 weeks)
CAD	Calcium score in asymptomatic patients		Acute chest pain with high enough suspicion of CAD
	Stable chest pain without high suspicion of CAD		Stable chest pain with high risk of cardiovascular events, or when high-risk anatomy is suspected
Structural cardiac disease	Patients with stable structural cardiac disease (TAVR, TMVR, LAA occlusion, together with the Heart Team)		Patients requiring urgent structural intervention (TAVI, TMVR, LAA occlusion)
Atrial fibrillation	Assessment of pulmonary veins for planning atrial fibrillation ablation	Evaluation of the left atrial appendage in chronic atrial arrhythmia before restoring sinus rhythm	Evaluation of the left atrial appendage in acute atrial arrhythmia before restoring sinus rhythm
Heart failure	Investigation of CAD as cause of heart failure in patients with stable cardiomyopathy		Hospitalized patient with acute cardiomyopathy and low or intermediate probability of CAD, where CCT can change management
			Evaluation of left ventricular assist device malfunction
Valvular	Assessment of aortic stenosis severity	Subacute or chronic prosthetic valve dysfunction	Acute and symptomatic prosthetic valve dysfunction, endocarditis, perivalvular extension of endocarditis or possible abscess
Masses/ congenital	Suspected benign cardiac masses or those unlikely to require biopsy or surgical planning		New suspected malignant cardiac masses or those requiring biopsy or surgical planning
	Elective assessment of congenital anomaly		Ruling out left ventricle thrombus after inconclusive echocardiography, when alternative methods (magnetic resonance) are not available

CAD: coronary artery disease; TAVR: transcatheter aortic valve replacement; TMVR: transcatheter mitral valve replacement; LAA: left atrial appendage; CCT: cardiovascular computed tomography.

- Valves: basic anatomical assessment and color Doppler; in case of signs of dysfunction, evaluate further.
- Pericardium: assessment of thickening or effusion.

3.3.2. Focused Ultrasound – Indications, Protocols, and Main Findings

The focused ultrasound, also known as point-of-care cardiac ultrasound, is widely used as a support tool in the diagnosis, management, and monitoring of patients with COVID-19.²³ The biggest advantages of this technique in patients with COVID-19 include its general availability in urgency/emergency settings and ICUs, its high diagnostic accuracy, and the wide range of clinical information that can be obtained through this examination. The focused ultrasound is also easily performed as a bedside examination – avoiding patient transportation to the radiology service and virus spread within the hospital. This test can be performed both with conventional ultrasound equipment or with portable or ultraportable (pocket-sized) devices; these are preferred due to easier disinfection and bedside use. All personal and equipment protective measures previously described should be performed. Among the applications of focused ultrasound in patients with COVID-19, we highlight lung and cardiac ultrasonography.

3.3.3. Focused Lung and Pleural Ultrasonography

Lung ultrasound (LUS) represents a fast alternative for evaluating the degree of pulmonary involvement and monitor the result of therapeutic interventions at the bedside. The diagnostic accuracy of LUS is similar to that of chest computed tomography (CT) in patients with respiratory complaints such as dyspnea and hypoxemia (85% sensitivity, 93% specificity for non-COVID-19 pneumonia).²⁴ Normal LUS findings have also presented an excellent correlation with chest CT results with no alterations of lung parenchyma such as ground-glass opacities. Therefore, LUS presents a high negative predictive value, allowing its use in patient risk stratification.²⁵ In addition to diagnosis and initial risk stratification, LUS is being widely used in the monitoring of critically ill patients COVID-19.²⁶ It contributes to decision-making on prone ventilation, extracorporeal membrane oxygenation (ECMO), and weaning from mechanical ventilation in acute respiratory failure.²⁷ LUS is also useful for ruling out other pathologies such as pneumothorax, which can occur in individuals on positive pressure ventilation.

Various LUS protocols are described in the literature. Regarding patients with COVID-19, at least 6 regions should be assessed in each hemithorax: anterior, anterior axillary

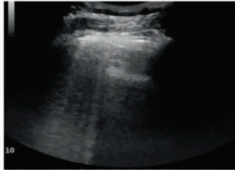
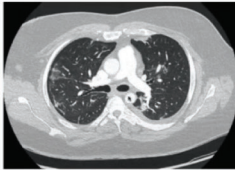
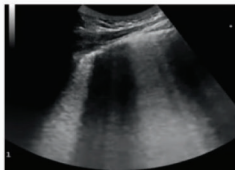
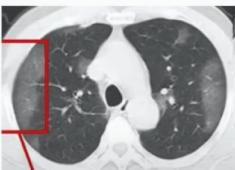
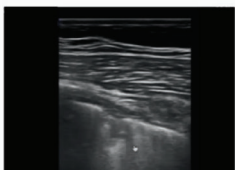
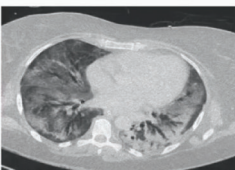
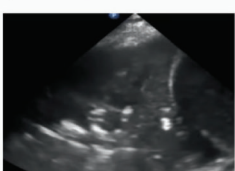
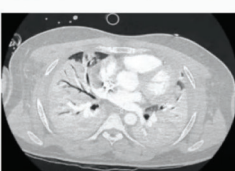
Statement

and posterior axillary regions above and below a line at the fourth intercostal space. Since COVID-19 lung affections are bilateral, multifocal, and not necessarily uniform, we highlight the importance of not focusing on specific areas of the thoracic wall and recommend a full chest assessment.^{28,29} LUS findings in patients with COVID-19 are able to monitor the progression and extension of pulmonary affections identified by the chest CT and are described in Figure 3. Notably, pleural effusion is not a common finding of COVID-19, hence it indicates a low probability of SARS-CoV-2 infection. Throughout the recovery period, the lungs gradually return to normal; ultrasound assessment indicates that subpleural consolidations disappear, the pleural line normalizes, and A-lines reappear.³⁰

3.3.4. Focused Cardiovascular Ultrasound

Focused cardiovascular ultrasound is being used by emergency physicians or intensivists for rapid assessment and screening for pre-existing cardiac and vascular diseases, as well as in the early detection of COVID-19-related myocardial alterations.²³ The objective of this ultrasound is to quantitatively assess left ventricular systolic function, right

ventricular size and contractility, inferior vena cava size and collapsibility, in addition to severe valvular abnormalities and pericardial effusion.²⁹ (Figure 4). A brief screening of patients with COVID-19 is indicated in the presence of high troponin and BNP in addition to electrocardiographic or hemodynamic changes, or in the case of suspected PE.³¹ In this case, one of the main advantages of focused ultrasound is that it reduces the need for conventional echocardiography, thus also decreasing the physicians' exposure and the need for equipment decontamination while also saving PPE. This examination is not equivalent to echocardiography, but it is capable of confirming or excluding a specific diagnosis during a quick bedside evaluation, thus contributing to therapeutic decisions. The focused ultrasound can also be used in the triage of patients that need echocardiography. On the other hand, without proper training, there is a risk of acquiring inadequate images that lead to false positive or false negative diagnoses. This could in turn result in unnecessary treatments that can be harmful, in inappropriate echocardiography indications, or in treatment delays. Therefore, the use of focused cardiac ultrasound should be based on institutional protocols, and we recommend an internal competence-

	Lung ultrasound	Chest CT	Ultrasound findings
Initial			Few, sparse B-lines Normal or thickened pleural line
Intermediate			Confluent B-lines Normal or thickened irregular pleural line
Severe			Confluent B-lines Thickened irregular pleural line, with subpleural consolidations
Extreme			Lung consolidations

The 12-area examination method is recommended – 6 areas in each hemithorax, divided in upper and lower (by a line in the fourth intercostal space) in anterior, anterior axillary and posterior axillary.

Figure 3 – Lung ultrasound findings in patients with COVID-19 and their correlation with disease severity and tomography findings

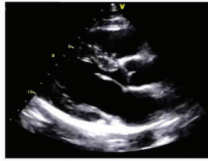
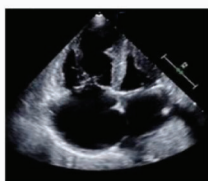
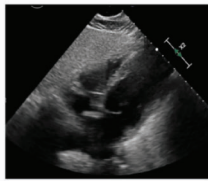
	Protocol	What to look for	Possible affections
Parasternal long-axis		Left ventricular size and systolic function Aortic and mitral stenosis or regurgitation	- Myocarditis - Cardiomyopathies
Parasternal short-axis		Left ventricular size and systolic function Shape of the left ventricle Movement and shape of the interventricular septum	- Stress cardiomyopathy - Cardiogenic shock - Pulmonary hypertension
Apical 4-chamber		Left and right ventricular chamber size and systolic function Tricuspid regurgitation and pulmonary artery systolic pressure	- Pulmonary thromboembolism - Myopericarditis
Subcostal		Pericardial stroke and signs of hemodynamic repercussion Pericardial stroke and signs of hemodynamic repercussion Inferior vena cava - Central venous pressure/fluid state - Thrombi	- Tamponade

Figure 4 – Protocols for the focused cardiovascular ultrasound. Windows, main findings, and possible diseases.

based certification as well as constant quality assessments, considering that teaching and training methodologies for this method vary greatly.

Integrated (lung and cardiac) focused ultrasound is ideal for adequate characterization of volume status, subjacent ventricular function, monitoring of fluid state, and titration of vasopressor drugs in case of inotropic support. In patients with RV dysfunction, focused vascular ultrasound for investigating deep vein thrombosis (DVT) can complete the assessment.

3.4. Prioritization and Indications for Stress Echocardiography in the COVID-19 Era

In patients at low risk for COVID-19, with proper indication and when deferring is not possible or recommended (such as in preoperative cancer patients or those with a high pre-test probability of obstructive coronary artery disease [CAD]), pharmacological stress tests are preferred because they are not considered aerosol-generating. Another alternative for investigating selected cases of chronic coronary arterial disease during the pandemic is to prioritize computed tomography (CT) coronary angiography.¹⁰ Once a very low local prevalence

of COVID-19 is reached, exercise echocardiography can return to being the first choice, but with additional safety procedures as previously described.

3.5. Prioritization and Indications for Transesophageal Echocardiography in Adult Patients in the COVID-19 Era

TEE causes additional concern, since the risk of equipment and professional contamination through droplets and aerosols is very high. Therefore, the incremental value of TEE in relation to transthoracic echocardiography (TTE) should be carefully evaluated on a case-by-case basis together with the assistant physician. For the duration of the pandemic, alternative methods should preferably be chosen, especially in patients with COVID-19.^{2,12} One of the main indications for TEE — screening for intracavitary thrombi — can be performed through CT angiography, which presents a lower risk of staff contamination. This alternative is obviously only available for patients who can be transported and with preserved renal function. Whenever possible, complete diagnosis should be achieved through TTE, leaving TEE for critical situations with possible changes in management, especially in the ICU or operation

Statement

room where no other methods are available and the clinical question should be promptly answered. In areas where the pandemic is decreasing, the reintroduction of TEE for outpatients should follow strict criteria, and each case should require an individual evaluation. It is recommended that outpatient scheduling be restored based on patient priority, considering one's previous position on the waiting list, clinical indications and conditions (symptomatic or asymptomatic), and potential impact of the examination in the patient's clinical history (for example, tests required for further procedure scheduling).^{2,12,13} Additional measures for TEE scheduling and test safety are described in Table 2. Among the various indications for TEE, high priority is given to the following:³²

- Infective endocarditis with valvular or paravalvular involvement.
- Type A aortic dissection (Stanford) in unstable patients (if stable, prefer CT; if associated with suspected aortic insufficiency, perform TTE).
- Beginning of mechanical circulatory support.
- Acute myocardial infarction with suspected mechanical complications not detected by TTE (ventricular septal defect, left ventricular free wall rupture, or papillary muscle rupture).
- Prosthetic valve dysfunction poorly defined in TTE or CT.
- Monitoring of patients on venovenous ECMO for treating COVID-19 pneumonia.
- Intraoperative evaluation of the result of mitral valve repair, septal myectomy, or in the diagnostic and management of complications.
- Hemodynamic instability due to undifferentiated shock in individuals with inadequate acoustic windows for TTE (such as those in the perioperative period of cardiac surgery or on prone ventilation).
- Screening for thrombi in the left atrial appendage prior to electrical cardioversion for restoring sinus rhythm in an unstable patient or with unavailable cardiovascular computed tomography (CCT) (CCT with low contrast infusion is the first choice for patients with COVID-19).

TEE is not recommended in the following cases:

- Screening for infective endocarditis in patients with transient fever and no bacteremia or new heart murmur.
- Transient bacteremia with identified pathogen not typically associated to infective endocarditis or with documented non-endovascular source of infection.
- Re-evaluation of a previous echocardiogram in stable individuals when no changes in therapy are being considered.

4. Pediatric, Congenital, and Fetal Echocardiography in the COVID-19 Era

The echocardiographic examination in children can result in increased risk for the staff and community, considering that although these patients have a reduced

occurrence of severe COVID-19, many infected children can be asymptomatic or minimally symptomatic. In addition, pediatric care requires the company of an adult, thus demanding adjustments in specialized care. Since the pediatric population with congenital heart defects is different from the corresponding adult one regarding the risk of COVID-19 transmission and indications for echocardiography, the aim of this topic is to update indications and protocols for TTE and FE in this population.

4.1. Prioritization and Indications for Transthoracic Echocardiography in Pediatric and Congenital Patients

Within the pediatric age group and considering patients with congenital heart defects, absolute indications include suspected congenital heart defect, postoperative and preoperative evaluation of congenital heart defects, children with acquired heart disease, heart transplant, increased risk of impaired cardiac function (chemotherapy treatment), and cardiac complications associated with respiratory infections.^{33,34} These indications should be categorized as high, medium, or low priority, as demonstrated in Table 2, when reintroducing examinations at the outpatient level according to the hemodynamic repercussions and clinical reasoning.

4.2. Optimization of the Transthoracic Echocardiography Protocol in Pediatric and Congenital Patients

TTE should be performed in the usual manner due to the wide anatomical variability and challenges regarding the evaluation of systolic and diastolic function, thus leaving focused assessment for other applications such as the emergency sector, pediatric intensive care, and in suspected of confirmed COVID-19 patients. In case of a potentially complicated examination, the patient should be referred to a more experienced physician; this increases the probability of an adequately detailed, precise, and quick examination without the need for additional practical support. Recently, an alert regarding multisystem inflammatory syndrome in children and teenagers has been released; this disorder has been described as a generally late clinical presentation associated with COVID-19, characterized by similar manifestations to those of the typical or incomplete Kawasaki syndrome and/or septic shock syndrome.³⁵ The most affected age range includes school-age children (mean age 9 years), which differentiates this disorder from the Kawasaki syndrome; symptoms are predominantly gastrointestinal. Virtually 100% of cases have heart affections with LVEF impairment, which has been described by various groups. In addition, patients present cardiogenic shock and coronary artery involvement with variable degrees of dilation, and some groups have reported aneurysms. Respiratory symptoms are mild, and skin rash and mucosal involvement may also occur.^{35,36} In case of clinical suspicion of multisystem inflammatory syndrome in children and teenagers, the main objectives of echocardiography are to identify possible left ventricular dilation, measure systolic function through LVEF, quantify the valvular regurgitation, evaluate the morphological aspect of coronary arteries (dilation and/or aneurysm), and pericardium.

4.3. Prioritization and Indications for Fetal Echocardiography

FE assessment faces challenges in the final stage of pregnancy where perinatal and neonatal planning and decision-making are required. At first, patients with low-risk pregnancies were instructed to not perform FE; those with moderate-risk pregnancies should defer FE for when the COVID-19 risk was reduced or until 28 weeks of pregnancy; finally, women with high-risk pregnancies should promptly schedule and perform the examination.¹⁵ However, as the pandemic progressed, considering that pregnancies would continue and fetal cardiac diseases can be critical, we recommend that FE be performed according to the previously published guidelines.^{37,38} The examination should be performed following PPE protocols for the pregnant patient and health care professional. Echocardiographic assessment should be as complete as possible, avoiding re-evaluations.

The possibility of prenatal or perinatal infection should be considered when newborns are transferred to the pediatric or cardiac neonatal intensive care unit after birth. Data on the vertical transmission of SARS-CoV-2 are still scarce;^{39,40} however, if the new mother tests positive for the virus in the 14 days after birth, the newborn should also be tested and managed as a positive case until a negative result is confirmed.

Echocardiographic tests in the pediatric population and in patients with congenital heart defects remain crucial during the SARS-CoV-2 pandemic and their health care should be guaranteed, minimizing risks for the professional team, patients, and the general public.

4.4. Prioritization and Indications for Transesophageal Echocardiography in Pediatric Patients

In patients with congenital heart defects, TEE is considered a part of intraoperative care and hemodynamic interventions. In outpatient cases, considering the high risk of exposure to SARS-CoV-2, this examination should be deferred or substituted for an alternative modality such as TTE associated with agitated saline contrast, cardiovascular computed tomography (CCT) or CMR with contrast agents. As for children, the risks and benefits of aerosol-emitting procedures should be weighed along with those of patient transportation, disinfection of the CCT/CMR room, contrast administration or radiation in CCT, in addition to prolonged exposure in case of CMR.

4.5. Protocol for Transesophageal Echocardiography in Pediatric Patients

Due to the unreliability of using symptoms in the prediction of COVID-19 status in children, a specific recommendation has been proposed for TEE in these patients:¹⁵

1. All pediatric patients should be considered positive for COVID-19 in TEE, unless with negative tests in the last 48 to 72 hours. In case of a negative test, TEE can be performed using standard precautions (gloves, mask, and eye protection).
2. In pediatric patients without negative COVID-19 tests in the last 72 hours, who were intubated before arriving to the operation room, the risk of producing aerosols is considered low. The probe can be introduced by the anesthesiologist or

examining physician, according to the institution's standard procedures and precautions.

3. In asymptomatic patients without negative COVID-19 tests in the last 72 hours who require intubation in the operation room, this procedure should be performed by the anesthesiologist using appropriate PPE and air purifying respirators. This process should be followed by a 20- to 30-minute waiting period, depending on local protocols and environmental factors, for allowing complete room air exchange. During this period, people should not be allowed in the room. The TEE probe should ideally be introduced by the anesthesiologist immediately after airway stabilization for minimizing the exposure of other professionals. After the waiting period, the examining physician can manipulate the probe according to standardized procedures and precautions.

4. Children with positive COVID-19 tests or with symptoms should be isolated. Probe introduction by the anesthesiologist is strongly advised for minimizing the exposure of other professionals. The team of health care professionals in the operation, recovery, or procedure rooms should use strict isolation equipment at all times and be trained in PPE donning and doffing. Only essential personnel are allowed in the operation room (only one echocardiography physician) for reducing exposure risk and saving PPE.

5. Vascular Ultrasonography in the COVID-19 Era

One of the situations requiring the biggest caution in patients infected by the SARS-CoV-2 virus is the development of coagulopathies, mostly characterized as a tendency for venous, arterial, and microvenous thrombosis. Klok et al.³¹ evaluated the incidence of venous thromboembolism (VTE) and arterial thrombotic complications in 184 patients with COVID-19 admitted to an ICU. Despite the VTE prophylaxis performed in all patients, a 31% incidence of thrombotic complications was observed.³¹ Accordingly, there was an increase in demand for vascular ultrasonography (VUS) during the pandemic, especially for the venous VUS in patients with COVID-19, most of which were hospitalized. For this reason, a deeper discussion on this examination is performed below.

5.1. Prioritization and Indications for Vascular Ultrasonography in Patients at Low Risk for COVID-19

Considering outpatients without COVID-19, the types of examinations should be categorized according to indication priority (see Table 1). High-priority (essential) examinations include venous VUS for DVT screening, as well as the carotid and vertebral artery VUS in patients with suspected stroke. Considering patients with peripheral obstructive disease, a priority for arterial VUS should depend on surgical treatment indications.

Other examinations should be categorized as medium or low priority by the assistant physician, as long as there are no indications for urgent invasive treatments. These include VUS of the aorta and its branches, VUS for varicose vein assessment, and carotid artery VUS in screening for carotid artery disease in the preoperative period of cardiac surgery.

Statement

5.2. Prioritization and Indications of Vascular Ultrasonography in Patients with COVID-19

- Suspected pulmonary thromboembolism (PTE): VUS has a low accuracy in diagnosing PTE, but can be indicated in case of high bleeding risk, when the result should change management, or when PTE suspicion is high and there is no available CT angiography.⁴¹
- Suspected DVT: In individuals with high clinical suspicion of DVT and bleeding risk, lower limb venous VUS is recommended.⁴¹
- Suspected acute arterial occlusion of upper or lower limb (arterial VUS).
- Stroke of unknown cause (carotid and vertebral artery VUS).

5.3. Situations Where Vascular Ultrasonography is Not Recommended for Patients with COVID-19

Venous VUS should not be used as a marker for altering a patient's anticoagulant therapy management.

Laboratory tests cannot indicate the need for this examination; hence, high D-dimer values do not justify VUS for DVT screening. In case of negative D-dimer results, there is no need for VUS in DVT screening.

Upper limb DVT has low morbidity in critically ill patients, thus there is no routine recommendation for venous VUS in this region.

In conclusion, VUS is not recommended in situations where its results will not determine changes in management or are not a prerequisite for urgent surgery.

5.4. Optimization of Vascular Ultrasonography Protocols

The complete venous VUS protocol is the recommended method for investigating DVT; however, point-of-care 3- or 2-point compression ultrasound in critically ill inpatients with COVID-19 seems to be a reasonable option, except if the pain reported by the patient is located in the infrapatellar segment (then, the complete protocol should be performed). The 3-point protocol assesses compressibility in all proximal veins of the evaluated lower limb. The 2-point protocol evaluates the compressibility of the common femoral vein 1 to 2 cm above and below the saphenofemoral junction (in the inguinal fold) and in the popliteal vein up to the confluence of the leg veins.⁴² Total or partial absence of compressibility in the affected vein, as well as vascular swelling due to an intraluminal thrombus detected by 2-dimensional techniques, are ultrasonographic signs of DVT. The sensitivity of the 3-point compression method is considered greater than that of the 2-point method (90.57% vs 82.76%), with similar specificity (98.52%).⁴³

In addition to a shorter exposure period for the professional, the point-of-care VUS protocol can be performed by the emergency physician, provided proper training is involved. After the pandemic, when possible, the complete protocol should be given preference.

Other VUS examinations, such as the carotid and vertebral artery VUS and limb arterial VUS, when necessary, should

follow previously established protocols.⁴⁴ All protective and PPE measures should be followed as previously discussed.

6. Cardiac Magnetic Resonance in the COVID-19 Era

6.1. Prioritization and Indications

The COVID-19 pandemic caused an important reduction in the number of outpatient requests for CMR, leaving only high-priority examinations: Clinical suspicion of myocarditis, differential diagnosis of cardiac masses, as well as other exceptional situations such as the assessment of complex ventricular arrhythmias.

CMR is well-defined as the preferred method for the reliable assessment of ventricular function, cardiac volumes, ischemia, myocardial viability, as well as in the detection of areas of myocardial fibrosis, study of infiltrative and deposition diseases, structural evaluation of patients with cardiac arrhythmias, and in specific cases, for complementing the echocardiographic evaluation of valvular and congenital heart diseases. In patients with low risk for COVID-19, prioritization should follow the rationale presented in Table 1. CMR has the advantage of providing, with one test, a global assessment of the heart with multiple functional and structural data, thus avoiding multiple trips to the hospital or clinic; this reduces patient circulation and optimizes resources.⁴⁵ In patients with COVID-19, CMR allows the diagnostic of myocarditis, perimyocarditis, acute myocardial infarction with no evidence of obstructive coronary artery disease (MINOCA), Takotsubo syndrome, and the differentiation between ischemic and inflammatory presentations. Conversely, the patient's risk of transmission and instability in the acute phase should be carefully evaluated and the examination could be deferred, whenever possible, until the criteria for cure are attained. On the other hand, a recent study evaluated myocardial injury in patients who had recovered from COVID-19 and showed a high prevalence of nonischemic delayed myocardial enhancement and preserved systolic function, already with no evidence of edema, suggesting permanent myocardial damage.⁴⁶ CMR can thus be an important tool for better comprehending the mechanisms of myocardial injury and for assessing myocardial damage after recovery from COVID-19.

6.2. Optimizing Cardiac Magnetic Resonance Protocols

CMR protocols should be reduced (maximum 30 minutes) for all clinical indications; the focus should be on evaluating myocardial function through cine magnetic resonance imaging (MRI), while myocardial tissue characterization should be performed through late gadolinium enhancement. A T2 weighted anatomical sequence can be performed for detecting myocardial edema in case of suspected acute myocardial inflammation. When available, T1, T2, and/or T2* mapping associated with cine MRI sequences and late enhancement

constitute an optimized and efficient protocol.¹¹ When evaluating myocardial ischemia, the physician should focus on perfusion sequences under pharmacological stress, subsequently adding cine and late enhancement sequences after stress. CMR can also be employed in the diagnosis of intracavitary thrombi, with a fast and directed study using late gadolinium enhancement and avoiding the need for TEE, thus reducing the examining physician's exposure to potential contamination. The evaluation of cardiac masses is adequately performed with high sensibility using CMR and can identify benign or malignant characteristics; it is though quite limited in the diagnostic of vegetations due to their small dimensions and mobile characteristics. Mass characterization should follow the routine protocol, which uses cine MRI sequences, T1 weighted anatomical sequences with or without fat suppression, T2, rest perfusion, and late enhancement, always focused on mass localization. Congenital diseases can have optimized assessment with the use of 3D resonance angiography associated with cine MRI sequences, and in case valve assessment is needed for complementing the echocardiography, ventricular function assessment through cine MRI should be prioritized and protocols should be directed to the valvular apparatus with flow mapping sequences.⁴⁷

7. Cardiovascular Computed Tomography in the COVID-19 Era

7.1. Prioritization and Indications

CCT can be used in the evaluation of multiple forms of heart diseases in all stages of the COVID-19 pandemic in a fast, efficient, and safe manner.⁴⁸ For this, depending on the local stage of the pandemic, the risk of exposure to the virus in the examination should be weighed with the benefit of its results for patient management and treatment.¹¹ Table 3 proposes the prioritization of indications during the COVID-19 pandemic.

As for indications, the main diagnostic and prognostic characteristics of CCT should be taken into consideration when making a decision:⁴⁹

- The ability of CCT to precisely exclude high-risk CAD can prevent admissions and save resources, as well as recommend hospitalization for patients with detected disease (especially those reluctant to seeking emergency care).
- The fundamental role of CCT in the preoperative anatomical assessment of structural cardiac diseases reduces the risk of acute and chronic complications associated with interventions.
- CCT can be preferred over TEE for ruling out thrombi in the left atrial appendage and intracavitary thrombi before cardioversion, reducing chances of cough and aerosol generation related to TEE.
- In patients suspected or confirmed for COVID-19, the benefits of CCT in most clinical scenarios should not exceed the risks of exposure and infection of the personnel. Each case should be evaluated individually.

8. Nuclear Cardiology in the COVID-19 Era

Nuclear cardiology has a solid knowledge base on clinical experience, as well as diagnostic and prognostic values. All procedures in this area have the advantage of using widely automated protocols and equipment, which allows less contact between the health care professional and the patient. Moreover, except for exercise myocardial scintigraphy and ventilation/perfusion scintigraphy, no other nuclear medicine methods generate aerosols.⁵⁰ These aspects could reduce exposure to the virus and infection propagation while also saving precious resources.⁵¹

8.1. Prioritization and Indications

Nuclear cardiology has a superior role in the pandemic scenario considering patients without COVID-19. The rationale for prioritizing examinations should be as described in Table 2. The main indications include:¹¹

- Evaluating ischemia in patients with known CAD.
- Evaluating patients with chest pain syndromes. It is particularly useful for patients who are poor candidates for non-invasive anatomical imaging (such as those with stents or coronary artery calcification, who are allergic to contrast agents, or have a risk of impaired renal function).
- Evaluation of myocardial viability.
- Screening for amyloidosis.
- Identification of the inflammatory stages of sarcoidosis.
- Identification of infections in implanted devices.

On the other hand, a nuclear cardiology assessment is generally not necessary in the treatment of acute heart disease in patients with COVID-19. Ventilation scans or exercise stress tests should be omitted in areas going through the peak phase of the pandemic and/or in any patient with a known or suspected COVID-19 infection due to the high risk of aerosol emission.⁵² Specific considerations on the ventilation/perfusion scintigraphy protocol are described below.

8.2. Ventilation/Perfusion Scintigraphy

Currently, the gold standard for ruling out PE in patients with COVID-19 is the CT pulmonary angiography. However, this method cannot be used in patients with contraindications for iodinated contrast agents. A potential alternative relies in lung perfusion single-photon emission computed tomography (SPECT) using macroaggregated albumin tagged with ^{99m}Tc. Due to the high risk of aerosol production associated to ventilation scintigraphy (aerosols tagged with ^{99m}Tc), the American Society of Nuclear Medicine and Molecular Imaging discouraged the classical combination of ventilation/perfusion images in patients with COVID-19.⁵³ Ventilation scans should be omitted in patients with known or suspected COVID-19; therefore, the use of perfusion lung scintigraphy associated with chest CT or X-ray has been proposed.⁵⁴

For optimizing protocols amidst the pandemic, one should follow good imaging practices that allow for a safe and efficient examination, as already described; these include mainly:

Statement

- Performing protocols that minimize the procedure duration without affecting test precision, eg, only using imaging stress tests when indicated.
- Avoiding protocols that may generate aerosols – give preference to pharmaceutical stress over exercise stress whenever possible.

Figure 5 is a proposition that summarizes the general protocol for reintroducing cardiovascular imaging examinations. Firstly, it is necessary to define whether the test is essential at any given moment. If it is essential (urgent or high-priority), define whether the patient has a high risk for COVID-19 and which method would lead to the lowest risk of exposure, even with the use of PPE. In case the examination is not essential/urgent, evaluate the local stage of the pandemic: when the area is at the peak stage, defer lower priority examinations. If the pandemic is decelerating in the area in question, reintroduce test scheduling according to the patient's risk for COVID-19 and indication priority, within appropriate criteria; finally, define PPE and patient flow according to COVID-19 risk and type of test. Tables 1, 2, and 3 summarize the indication prioritization, safety protocols, and PPE to be used according to the type of test and COVID-19 status. Among cardiovascular imaging examinations, echocardiography is considered first-line. However, in view of the need for minimizing the examining physician's exposure to SARS-COV-2 and rationally using available resources, alternative methods can be used to answer the clinical question, especially in stable patients or

those with uncertain symptoms or who were referred to other imaging examinations.⁸

9. Conclusion

The COVID-19 pandemic has forced the medical community to reconsider performing cardiovascular imaging examinations. Adaptations and changes were necessary due to the worldwide impact of this pandemic. The return to “normality” in cardiovascular imaging services should be progressive and adapted to regional differences within the country. Considering the impact of cardiovascular diseases in the population morbidity and mortality, cardiovascular signs and symptoms cannot be neglected. Therefore, even amid a pandemic situation where all attention is turned to fighting COVID-19, patients and physicians should be encouraged to perform cardiovascular investigations and be assured that these will happen in a safe environment. This position statement reflects the opinion of specialists based on national and international guidelines and the scientific evidence available at the moment, seeing that knowledge on COVID-19 is constantly evolving. In this environment, recommendations can guide the health care team and protect patients and professionals without compromising care. In addition, these recommendations, the constant dialog between medical imaging specialists, clinical staff, and patients constitutes the best and most efficient measure for facing the COVID-19 pandemic.

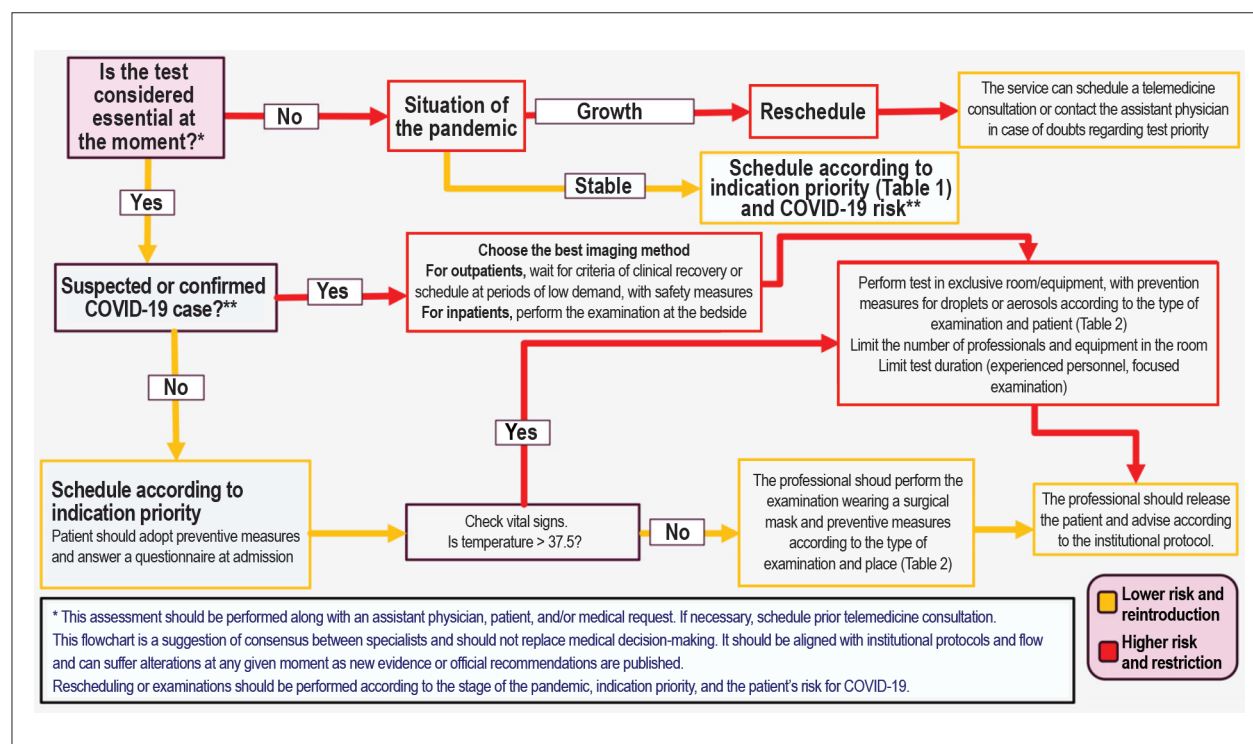


Figure 5 – Flowchart for reintroducing cardiovascular imaging examinations in the COVID-19 era

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