ABC Cardiol
Arquivos Brasileiros de Cardiologia

Volume 116 | Number 4
April 2020

Brazilian Society of Cardiology
ISSN-0066-782X

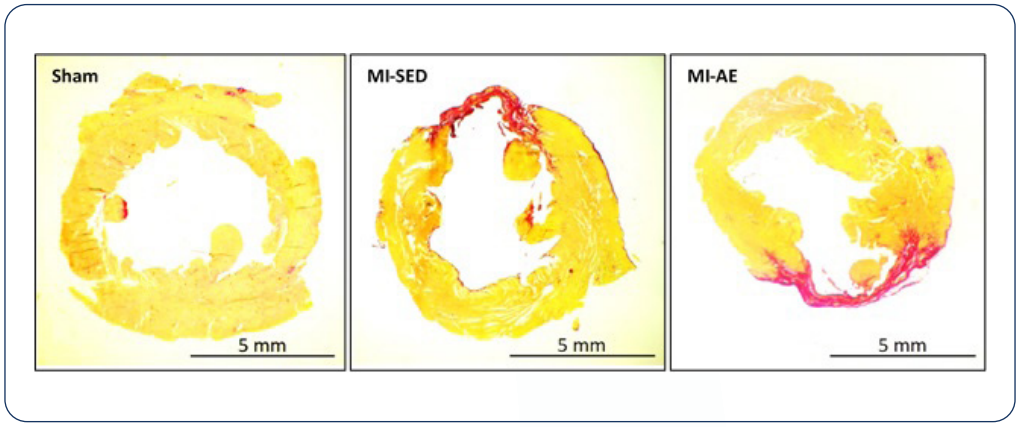


Figura 1, page 787

ABC Cardiol
Arquivos Brasileiros de Cardiologia
JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

Contents

ABC Cardiol

Arquivos Brasileiros de Cardiologia

JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

Sociedade Brasileira de Cardiologia

President
Marcelo Antônio Cartaxo Queiroga Lopes

Vice President
Celso Amodeo

Financial Director
Ricardo Mourilhe Rocha

Scientific Director
Fernando Bacal

Managing Director
Olga Ferreira de Souza

Service Quality Director
Sílvio Henrique Barberato

Communication Director
Harry Corrêa Filho

Information Technology Director
Leandro Ioschpe Zimerman

Governmental Relations Director
Nasser Sarkis Simão

State and Regional Relations Director
João David de Souza Neto

Cardiovascular Health Promotion Director – SBC/Funcor
José Francisco Kerr Saraiva

Director of Specialized Departments
Andréa Araujo Brandão

Research Director
David de Pádua Brasil

Coordinator of Science, Technology and Innovation
Ludhmila Abrahão Hajjar

Coordinator of Continued Medical Education
Brivaldo Markman Filho

Coordinator of Management Supervision and Internal Control
Gláucia Maria Moraes de Oliveira

Coordinator of Compliance and Transparency
Marcelo Matos Cascudo

Coordinator of Strategic Affairs
Hélio Roque Figueira

Editor-in-Chief of the Arquivos Brasileiros de Cardiologia
Carlos Eduardo Rochitte

Editor-in-Chief of the IJCS
Claudio Tinoco Mesquita

Coordinator of the University of the Heart
Evandro Tinoco Mesquita

Coordinator of Standards and Guidelines
Brivaldo Markman Filho

Presidents of State and Regional Brazilian Societies of Cardiology:
SBC/AL – Carlos Romerio Costa Ferro

SBC/AM – Kátia do Nascimento Couceiro

SBC/BA – Gilson Soares Feitosa Filho

SBC/CE – Gentil Barreira de Aguiar Filho

SBC/DF – Alexandra Oliveira de Mesquita

SBC/ES – Tatiane Mascarenhas Santiago Emerich

SBC/GO – Leonardo Sara da Silva

SBC/MA – Mauro José Mello Fonseca

SBC/MG – Henrique Patrus Mundim Pena

SBC/MS – Gabriel Doreto Rodrigues

SBC/MT – Marcos de Thadeu Tenuta Junior

SBC/NNE – Nivaldo Menezes Filgueiras Filho

SBC/PA – Dilma do Socorro Moraes de Souza

SBC/PB – Lenine Angelo Alves Silva

SBC/PE – Fernando Ribeiro de Moraes Neto

SBC/PI – Luiz Bezerra Neto

SBC/PR – Raul DAurea Mora Junior

SOCERJ – Wolney de Andrade Martins

SBC/RN – Maria Sanali Moura de Oliveira Paiva

SOCERON – Daniel Ferreira Mugrabi

SOCERGS – Mario Wiehe

SBC/SC – Amberson Vieira de Assis

SBC/SE – Eryca Vanessa Santos de Jesus

SOCESP – João Fernando Monteiro Ferreira

Presidents of the Specialized Departaments and Study Groups

SBC/DA – Antonio Carlos Palandri Chagas

SBC/DCC – Bruno Caramelli

SBC/DCC/CP – Klebia Magalhães Pereira Castello Branco

SBC/DCM – Celi Marques Santos

SBC/DECAGE – Izo Helber

SBC/DEIC – Evandro Tinoco Mesquita

SBC/DERC – Gabriel Leo Blacher Grossman

SBC/DFCVR – Antoinette Oliveira Blackman

SBC/DHA – Audes Diógenes de Magalhães Feitosa

SBC/DIC – Carlos Eduardo Rochitte

SBCCV – Eduardo Augusto Victor Rocha

SOBRAC – Ricardo Alkmim Teixeira

SBHCI – Ricardo Alves da Costa

DCC/GAPO – Danielle Menosi Gualandro

DCC/GECETI – Luiz Bezerra Neto

DCC/GECO – Roberto Kalil Filho

DCC/GEMCA – Roberto Esporcatte

DCC/GERTC – Adriano Camargo de Castro Carneiro

DEIC/GEICPED – Estela Azeka

DEIC/GEMIC – Marcus Vinicius Simões

DERC/GECESP – Clea Simone Sabino de Souza Colombo

DERC/GECN – Lara Cristiane Terra Ferreira Carreira

DERC/GERCPM – Carlos Alberto Cordeiro Hossri

GECIP – Marcelo Luiz da Silva Bandeira

GEECG – Carlos Alberto Pastore

DCC/GETA – Carlos Vicente Serrano Junior

DCC/GECRA – Sandra Marques e Silva

Arquivos Brasileiros de Cardiologia

Volume 116, Nº 4, April 2021

Indexing: ISI (Thomson Scientific), Cumulated Index Medicus (NLM), SCOPUS, MEDLINE, EMBASE, LILACS, SciELO, PubMed

Address: Av. Marechal Câmara, 160 - 3º andar - Sala 330
20020-907 • Centro • Rio de Janeiro, RJ • Brasil
Phone.: (21) 3478-2700
E-mail: arquivos@cardiol.br
http://abccardiol.org/
SciELO: www.scielo.br

Commercial Department
Phone: (11) 3411-5500
E-mail: comercialsp@cardiol.br

Editorial Production
SBC - Internal Publication Department

Graphic Design and Diagramming
SBC - Internal Design Department

Affiliated at the Brazilian Medical Association

SUPPORT

Ministério da **Educação**

Ministério da **Ciência e Tecnologia**

Radi Macruz — The Legacy of an Icon

Edmar Atik,[1] *Charles Mady,*[1] *Jose Antonio Franchini Ramires*[1]

Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo,[1] *São Paulo, SP - Brazil*

Radi Macruz, Associate Professor in the Department of Cardio-Pulmonology at Faculdade de Medicina da Universidade de São Paulo, died in São Paulo on November 30, 2020, at the age of 95.

He was born on July 5, 1925 in São Paulo, son of the Lebanese couple Kalil and Nini Macruz. Attended medical school at FMUSP and became the great pioneer physician, introducing many advances that made him one of the most relevant icons. He was an idealizer in pursuit of the most appropriate dynamics of science and scientific discoveries.

His academic history has always been based on deep knowledge and the progress of cardiology sciences as a whole.

Encouraged by his father, who stressed the importance of doctors in society, he started medical studies at Universidade de São Paulo in 1946, even though Mathematics had been his passion since he was a young man, from his studies in schools in the interior of São Paulo, where he lived with ten more siblings, in addition to the seven cousins, from his paternal uncle.

However, in his professional career, it was Mathematics that influenced his scientific work in Cardiology, interconnected on many levels. This resulted in the creation of a namesake index — the PPR interval in electrocardiography — for the characterization of atrial overloads.[1-4]

Once, for this creation and so many others, Instituto do Coração (InCor) received one of the greatest electrocardiography authorities in the world, South African Leo Schamroth,[5,6] to give a lecture. Escorted by Dr. Charles Mady to the seminar room, Mr. Schamroth met Macruz at the door. When introduced to Macruz, Mr. Schamroth asked if he was the Macruz index one. Mr. Mady replied yes, then hurried to open his book and show the page by commenting on the said index. They both became friends. Macruz did not need any great technologies to show his genius.

He believed that there is no Medicine without Humanism, that the passion of life was the discovery of different things, that critical mass leads to thinking and development, that logic reaches the truth, that the spirit of research is nothing more than questioning itself, that passion unravels the mysteries of nature (Figure 1).

Keywords

Radi Macruz; Cardiologists/trends; Faculty; Physicians; Cardiology; Ethics, Medical.

Mailing Address: Edmar Atik •
Rua Dona Adma Jafet, 74, cj.73. Postal Code 01308-050, Bela Vista, São Paulo, SP - Brasil
E-mail: edmaratik@uol.com.br
Manuscript received December 17, 2020, revised manusript February 03, 2021, accepted February 03, 2021

DOI: https://doi.org/10.36660/abc.20201341

Since returning from the United States, where he participated in a study group with his friend Sarnoff,[7] he has become an inexhaustible source of ideas and scientific production. As he had a very broad general education, he did not limit himself to creating in subspecialties, which was too little for him, as he had a solid background in mathematics and statistics, which helped him a lot.

With all these directions in life, he started to try to understand Pediatric Cardiology, a specialty that involved a lot of diagnostic and therapeutic difficulties, especially in the 1950s and 1980s. In that period, he educated himself with Munir Ebaid, and became one of those responsible for the worldwide recognition of this specialty, as a Brazilian icon.

He innovated with the treatment of pulmonary hypertension in congenital heart diseases, with the opening of an atrial septal communication. He introduced original concepts about the individual normality of blood pressure. He wanted to perform transposition of the great arteries in patients with heart failure, with a normal right ventricle.

He was so knowledgeable that everyone would looking for him to get help with management difficulties. He would then start his medical visits, always with a lot of interested people, as his discussions at the bedside were anthological and highly sought-after. He diagnosed complex cardiopathies at the bedside, with physical examination, simple radiology and electrocardiography, merely based on clinical reasoning. He was one of the very few doctors who were not afraid of exposing their thoughts in a clinical discussion, when people would often find it nonsense and, later, would bow to a shining light.

For this reason and with such motivation when entering the ward at Hospital das Clínicas or Instituto do Coração, he would turn off the lights then say that "the light had arrived".

No wonder in 1983 he released the first specialty book in Brazil, entitled "*Cardiologia Pediátrica*" (Pediatric Cardiology), with Dr. Rachel Snitcowsky, published by Editora Sarvier.[8] Then, he entered the general field of Cardiology and his flair for investigation was such that he associated the site of chest pain with the coronary artery affected, in addition to establishing the spatial distribution of this circulation. While doing these investigations, he would jokingly say that the obstruction of coronary arteries would also cause a heart murmur in the chest. Even from this unrecognized statement, his leading role in unceasing scientific search would be further cemented.

He described the tortuosity of coronary arteries as the cause of ischemia. Once, he suggested to provoke an interventricular septal infarction decrease and/or eliminate a right and/or left ventricular outflow tract obstruction into hypertrophic cardiomyopathy, for the uneasiness of his peers at the time. Today, it is one of the procedures used in this disease.

Co-authoring with his wife Valéria Bezerra de Carvalho, he shared valuable information in the book "*Cardiopatia*

Figure 1 – *Photo of Radi Macruz, in the expression of seriousness and responsibility, resulting from thinking focused on possible scientific discoveries.*

Isquêmica-Aspectos de Importância Clínica" (Ischemic Heart Disease — Aspects of Clinical Importance), published by Editora Sarvier,[9] in 1989. In this book, he introduced new concepts about cardiac pain, relating the affected wall to the topography of pain, in addition to new concepts about intracavitary pressures.

As a pioneer and to enhance his typical historical marks, he suggested to conduct a heart transplant surgery in São Paulo, not performed due to legal impediments at the time, one year before the South African Christian Barnard performed the first surgery in the world. The surgery took place on December 3, 1967 at 5.25 am in Cape Town at the Grute-Schuur Hospital. Always hand in hand with progress, he encouraged surgeon Euryclides de Jesus Zerbini to perform the first acute myocardial infarction surgery in 1970, and got involved with the first coronary artery laser unblocking procedures in 1976. In the meantime, due to his involvement in further discoveries in the operative field, the prominent surgeon Adib Jatene called him "one of the fathers of cardiac surgery in Brazil". His connection with other fields, as an astute general practitioner, allowed him to state openly that "if surgery was a difficult thing, it would be performed by the general practitioners," which amused everyone, as his statement reaffirmed the brilliant performance of general practitioners. He was also a pioneer in the introduction of echocardiography in Brazil in 1970, which greatly supported diagnosis in pediatric cardiology, which underwent consistent changes, especially in the diagnostic and therapeutic, clinical and surgical fields.

In addition, he actively participated in the construction of Instituto do Coração, opened in 1978, which became another scientific enhancement facility of Hospital das Clínicas da Universidade de São Paulo.

With Luiz Décourt, Fúlvio Pillegi, João Tranchesi, E J Zerbini, Geraldo Verginelli, Delmond Bittencourt, Egas Armelin, and others, he built the golden phase of Cardiology and the fruits today are harvested by so many disciples who have also become names of prominence, such as the Full Professor of Cardiology Jose Antonio Franchini Ramires.

Complementing his cultural power, he wrote a book that drew attention to the characterization of his capacity, when he actually connected Mathematics, his declared passion, to Medicine. The title "*Matemática da Arquitetura Humana – Idiometria Humana – Novos Rumos da Normalidade"* (Mathematics of Human Architecture — Human Idiometry — New Directions of Normality),[10] presents the thesis of normality patterns and outlines the functioning of the human body guided by the rules of Mathematics. And he explains that "normal is what something has to be, it is the truth to be reached: it cannot be an interval; it is one and only one number and, to obtain it, one must know the golden dominant explanatory, therefore universal and basic variable."

Based on these concepts, Macruz explains what normality means, defines what is normal, then shows what to treat, when to treat and where to treat, considering racial, cultural and dietary variations influenced by perception.

Of a solid background, he was one of the greatest general practitioners of our times. He set trends and had disciples around the world, who admired and still admire him greatly. This is the greatest legacy that a Master can leave.

Editorial

A brilliant doctor, tireless thinker of solutions for different heart diseases, he was not a scientist, but a doctor with an excellent background, who used knowledge from different areas in order to understand or treat heart diseases. As such, he mixed up mathematics, physics, biology and philosophy, seeing the world and medicine in a broad and comprehensive way, without denying doctors' responsibility for getting more and more information about their patients and their disease. He was never happy with whatever was available and, for this reason, he would jokingly announce "the light has arrived," sharing ideas that often seemed absurd, but over the years have come to exist as solutions in clinical practice.[11]

Like Décourt, he had a solid cultural background. Literature, music, art, everything was part of his daily life. He was not only a doctor and a researcher, but a human being with enormous curiosity. We were his disciples, and we are definitely proud of him. When he retired, the Medical School and Incor lost an academic piece. However, we kept in touch and his ideas continued to flow.

His personal characteristics made him unmistakable, so we would easily know when he was coming in. Our relationship was much more than professional, as we were all very close friends, and he ended our conversations, from the height of his wisdom, with the words "got it?", with his typical deep voice. Or, at the beginning of our conversations, he would say "the light has arrived," with a great sense of humor.

Dear friend, wherever you are, now you are around Décourt and Zerbini, and certainly creating. You have proved that the human being is viable. Radi, we miss you terribly.

One of the most brilliant masters that cardiology has ever produced, Radi Macruz, leaves us all. It is not easy to describe him humanly, and as an academic. In both sectors, his brilliance was indisputable. He had a complex and brilliant personality, so it was not easy to know him well.

Radi Macruz, your life was full of achievements, resulting from logic, in the midst of medical and human ethics, and your saying "GOT IT?" is left as a question in the pursuit of truth and assertion. We miss you as we all know that this longing is a source of encouragement.

Macruz, be sure that you have marked generations that will never forget you and every time we enter InCor's classroom, called the Macruz Room, the light will be on with the brilliance of rays of light, left by you.

References

1. Nicaise J, Lardani H, Van Houte C, Bernard R. Normal values of the Macruz index in children and adults. Study of the Macruz index in chronic pulmonary diseases (correlation with hemodynamic data). Acta Cardiol.1972; 27(3): 307-15.
2. Human GP, Snyman HW. The value of the Macruz index in the diagnosis of atrial enlargement. Circulation 1963; 27: 935-8.
3. Ferrer ST, Posada AE, Valbuena JF. Macruz's index. Its value in the electrocardiographic diagnosis of auricular enlargement. Rev Esp Cardiol. 1967; 20(1): 48-56.
4. Tronconi L, Specchia G. Analysis of the relationship of the P wave and P-Q segment or the Macruz Index and its clinical importance. Mal Cardiovasc. 1964; 5: 127-37.
5. Schamroth CL. Leo Schamroth (1924-1988): his life and work. J Med Biogr. 1996; 4(3): 125-8.
6. Millar RS. Leo Schamroth: his contributions to clinical electrocardiography – with reference to: incomplete left bundle branch block. Cardiovasc J Afr. 2009; 20(1): 28-9.
7. Lowenstein CJ, Weisfeldt ML, Mitchell JH. Sarnoff Cardiovascular Research Foundation: inspiring the physician-scientists of tomorrow. Circulation. 2018; 138(6): 554-6.
8. Macruz R, Snitcovsky R. Cardiologia Pediátrica. São Paulo: Sarvier; 1983.
9. Carvalho VB, Macruz R. Cardiopatia Isquêmica – Aspectos de Importância Clínica. São Paulo: Sarvier; 1989.
10. Macruz R. Matemática da Arquitetura Humana – Idiometria Humana. Novos Rumos da Normalidade. São Paulo: Roca, 2010.
11. Macruz R, Zerbini EJ, Décourt L. Infarto do Miocárdio Tratado com Intervenção Inédita em São Paulo. Folha de São Paulo; 1970. Disponível em: https://cutt.ly/Tl8BnWF. Acesso em: 3 mar 2021.

Neurological Complications in Patients with Infective Endocarditis: Insights from a Tertiary Centre

Sofia Alegria,[1] Ana Marques,[1] Inês Cruz,[1] Ana Luísa Broa,[1] Ana Rita F. Pereira,[1] Isabel João,[1] Otília Simões,[1] Hélder Pereira[1]

Hospital Garcia de Orta EPE – Cardiologia,[1] Almada – Portugal

Abstract

Background: Neurological complications are common in patients with infective endocarditis (IE). Recent data suggest that neurologic events are a major determinant of prognosis, and that surgery is critical in improving the outcome.

Objective: To characterize patients with IE and neurological complications and to determine predictors of embolization to the central nervous system (CNS) and mortality.

Methods: Retrospective analysis of patients admitted to a tertiary center with the diagnosis of IE from 2006 to 2016. Statistical significance was defined by a p-value < 0.05.

Results: We identified 148 episodes of IE, 20% of which had evidence of CNS embolization. In patients with CNS embolization, 76% presented with ischemic stroke. During follow-up, 35% were submitted to surgery and both in-hospital and one-year mortality were 39%. These patients had longer hospitalizations, but there were no significant differences regarding mortality in patients with and without CNS embolization. The independent predictors of neurological complications were diabetes (p=0.005) and the absence of fever at presentation (p=0.049). Surgery was associated with lower mortality (0 vs. 58%; p=0.003), while patients with septic shock had a poorer prognosis (75 vs. 25%; p=0.014). In multivariate Cox regression, human immunodeficiency virus (HIV) infection was the only independent predictor of in-hospital and 1-year mortality (p=0.011 in both).

Conclusions: In this population, embolization to the CNS was common, more often presented as ischemic stroke, and was associated with longer hospitalization, although without significant differences in mortality. In patients with CNS embolization, those submitted to surgery had a good clinical evolution, while patients with septic shock and HIV infection had a worse outcome. These results should be interpreted with caution, taking into consideration that patients with more severe complications or more fragile were probably less often considered for surgery, resulting in selection bias. (Arq Bras Cardiol. 2021; 116(4):682-691)

Keywords: Endocarditis, Infectious/surgery; Endocarditis,Infectious/complications; Central Nervous System/complications; Stroke; Embolization; Prognosis; Mortality

Introduction

Neurological complications are common in infective endocarditis (IE), occurring in 15–30% of patients.[1-3] Clinical presentation is variable and may include multiple symptoms or signs, though there is a predominance of focal signs and ischemic strokes are more often diagnosed. Transient ischemic attack, intracerebral or subarachnoidal hemorrhage, brain abscess, meningitis, and toxic encephalopathy are also observed, and firm evidence supports that additional clinically silent cerebral embolisms occur in 35–60% of IE patients.[4-6] Sepsis-related encephalopathy, defined by acute confusion or delirium, with varying levels of consciousness, may also contribute to neurological manifestations of IE.[7]

Mailing Address: Sofia Alegria •
Hospital Garcia de Orta EPE – Cardiologia - Avenida Torrado da Silva 2805-267 Almada - Portugal
E-mail: asofia.alegria@gmail.com
Manuscript received January 18, 2019, revised manuscript November 24, 2019, accepted December 27, 2019

DOI: https://doi.org/10.36660/abc.20190586

According to this, one should always consider IE in the differential diagnosis of patients with acute cerebral event and signs of systemic infection or history of undetermined febrile syndrome, keeping in mind that early diagnosis and the implementation of adequate antibiotic treatment can reduce the risk of recurrent embolization.[1]

Risk factors for central nervous system (CNS) embolization are well-known and include vegetation size and mobility,[2,8-10] *Staphylococcus aureus* infection,[11] and mitral valve involvement.[10] Nevertheless, the risk of CNS embolic events in IE decreases dramatically after the initiation of effective antimicrobial therapy, to less than 1.71/1,000 patient-days in the second week.[12]

Neurological manifestations occur before or at the time of IE diagnosis in a majority of cases, but new or recurrent events can also take place later in the course of IE. Neurological complications are associated with excess mortality, as well as sequelae, particularly in the case of stroke[2,13] and affect both medical therapy[14] and the optimal timing for surgery.[15] Rapid diagnosis and initiation of appropriate antibiotics are of major importance to prevent a first or recurrent neurological

complication.[12] Early surgery in high-risk patients is the second mainstay of embolism prevention, while antithrombotic drugs have no function.[1] Recent data suggest that neurological events are a major determinant of prognosis, and that surgery has a central role in improving the outcome.

However, the occurrence of neurological complications raises questions regarding the timing of surgery, as the safety of cardiopulmonary bypass in patients with these events remains controversial. The decision should be individualized after multidisciplinary assessment, involving cardiologists, cardiac surgeons, neurologists, and infectious disease specialists. If possible, surgery should be delayed in patients with large ischemic events or hemorrhagic events. It has been suggested that surgery should be considered within the first 72 hours in patients with ischemic events and severe heart failure, otherwise after four weeks. Early surgery appears safe in patients with transient ischemic attacks or silent events.

Therefore, the aim of this study was to characterize patients with IE and neurological complications and to determine predictors of embolization to the CNS and of associated mortality.

Methods

Retrospective, observational study based on the analysis of medical records of patients admitted to a 500-bed tertiary care center without on-site cardiac surgery and diagnosed with IE from 2006 to 2016. A comparison between patients with and without neurological complications was performed. This study was approved by the Ethics Committee of the institution.

Study Design and Patients

Several variables were analyzed for the present study, including the date of IE diagnosis; patients' age and gender; risk factors; type of endocarditis (native valve, prosthetic valve or device-associated); valves affected; infecting microorganism; date, type, and recurrence of neurological complications; performance of surgery; and outcomes. Prosthetic valve endocarditis was considered early if it occurred within 1 year after valve implantation and late if it occurred thereafter.

IE episodes were evaluated retrospectively according to the modified Duke criteria. Only patients with criteria for definite or possible IE and no other explanation for the clinical picture were included. Relapses were considered as a single episode, while distinct episodes occurring in a single patient were included. Transthoracic echocardiography was performed in all patients, while transoesophageal echocardiography was performed in the majority of patients. Microbiological information was obtained from blood cultures and intraoperative heart tissue specimens, as well as from serological studies when blood cultures were negative.

Definitions

Neurological complications were classified into the following categories: ischemic complications, cerebral hemorrhage, mycotic aneurism, meningitis, and brain abscess. The diagnosis of ischemic and hemorrhagic complications was based on clinical and radiological data, derived from head computed tomography (CT) or magnetic resonance imaging (MRI), performed in accordance with clinical practice. The diagnosis of mycotic aneurysm was also supported by head CT angiography.

Indication for Surgery

The indication for cardiac surgery was determined by the attending physicians according to the guidelines of the European Society of Cardiology.[1] All patients with indication for surgery were discussed by the cardiac team (including cardiologists, cardiac surgeons and, when deemed necessary, other specialties, such as neurologists and infectious disease specialists), and the decision about the performance and timing of surgery was made. When indicated, surgery was performed in the referral cardiac surgery center defined by the national health care system (Department of Cardiac Surgery, Santa Maria University Hospital, CHULN, Lisbon, Portugal).

Statistical Analysis

Continuous variables are described as mean ± standard deviation or median and interquartile range (IQR), according to the assessment of normality with the Kolmogorov-Smirnov test. Categorical variables are reported as percentages and absolute numbers. A comparison between variables in different patient groups was performed with the Pearson X^2 test for categorical variables or the independent samples *t*-test or Mann-Whitney U test for continuous variables. Analysis of baseline characteristics, type of endocarditis, etiology, complications, and management was performed per episode, while analysis of mortality was performed per patient.

Variables associated or with a trend to association with CNS embolization ($p < 0.10$) were tested with univariate and multivariate logistic regression, in order to identify independent predictors of embolization in the overall population. In the sample of patients with CNS embolization, variables associated or with a tendency to be associated with in-hospital and one-year mortality ($p < 0.10$) were tested with univariate and multivariate forward stepwise Cox regression, to identify independent predictors of prognosis. Kaplan Meier survival curves were used to identify predictors of outcome, which were compared with the log-rank test.

All tests were two-sided and statistical significance was defined as $p < 0.05$. Statistical analysis was performed using IBM SPSS Statistics, version 24.0 (IBM Corporation, Armonk, NY, USA).

Results

We identified 148 IE episodes (occurring in 142 patients; four patients had two episodes and one patient had three episodes; relapses were considered as a single episode). The characterization of the total episodes is detailed in Table 1. The median follow-up was 161 days (IQR 34-1,358).

About one-third of them (34.5%; n = 51) presented evidence of systemic embolization, and the most frequent site was the CNS (19.6%; n = 29). Other embolization sites included peripheral circulation (4.1%, n=6), lungs (2.7%, n=4), coronary arteries (1.4%, n=2), and spleen (1.4%,

Table 1 – Characterization of all episodes of admissions due to endocarditis (n=148)

Characteristic	Overall episodes (n=148)	With CNS embolization (n=29)	Without CNS embolization (n=119)	p*
Age (years) – median (IQR)	64 (51-75)	65 (53-69)	63 (50-75)	0.631
Age ≤ 75 years – n (%)	117 (79.1)	27 (93.1)	90 (75.6)	0.038
Male – n (%)	111 (75.0)	22 (75.9)	89 (74.8)	0.905
Previous history – n (%)				
Known valvular heart disease	72 (49.0)	15 (51.7)	57 (48.3)	0.741
Arterial hypertension	76 (51.4)	16 (55.2)	60 (50.4)	0.646
Diabetes mellitus	28 (19.2)	11 (37.9)	17 (14.5)	0.004
Coronary artery disease	21 (14.2)	6 (20.7)	15 (12.6)	0.263
Heart failure	40 (27.0)	4 (13.8)	36 (30.3)	0.074
Chronic kidney disease	22 (14.9)	4 (13.8)	18 (15.1)	0.856
Intravenous drug users	19 (12.9)	3 (10.3)	16 (13.6)	0.644
HIV infection	20 (13.6)	2 (6.9)	18 (15.3)	0.240
Invasive procedure in the preceding 3 months	54 (45.0)	10 (43.5)	44 (45.4)	0.870
Type of endocarditis - n (%)				
Health care-associated endocarditis	34 (23.3)	9 (31.0)	25 (21.4)	0.270
Prosthetic valve endocarditis	37 (25.0)	9 (31.0)	28 (23.5)	0.403
Implanted cardiac device endocarditis	5 (3.4)	1 (3.4)	4 (3.4)	0.981
Affected valve – n (%)				
Aortic	84 (56.8)	19 (65.5)	65 (54.6)	0.288
Mitral	58 (39.2)	13 (44.8)	45 (37.8)	0.488
Tricuspid	20 (13.5)	0 (0.0)	20 (16.8)	0.018
Symptoms / signs at presentation – n (%)				
Fever	102 (70.3)	16 (55.2)	86 (74.1)	0.045
Heart murmur	81 (56.3)	14 (50.0)	67 (57.8)	0.458
Microorganism – n (%)				
Staphylococcus sp	49 (33.1)	8 (27.6)	41 (34.5)	0.481
Staphylococcus aureus	36 (24.3)	6 (20.7)	30 (25.2)	0.611
Streptococcus sp	43 (29.1)	9 (31.0)	34 (28.6)	0.793
Streptococcus bovis	14 (9.5)	3 (10.3)	11 (9.2)	0.856
Streptococcus viridans group	18 (12.2)	2 (6.9)	16 (13.4)	0.333
Enterococcus sp	18 (12.2)	3 (10.3)	15 (12.6)	0.738
Gram negative bacteria	6 (4.1)	1 (3.4)	5 (4.2)	0.854
Fungi	3 (2.0)	1 (3.4)	2 (1.7)	0.545
BCNIE	30 (20.3)	6 (20.7)	24 (20.2)	0.950
Complications – n (%)				
Perivalvular abscess	20 (14.8)	4 (14.8)	16 (14.8)	1.000
Pseudoaneurism	7 (5.2)	2 (7.4)	5 (4.6)	0.560
Fistula	6 (4.4)	1 (3.7)	5 (4.6)	0.835
Acute heart failure	71 (48.0)	15 (51.7)	56 (47.1)	0.652
Septic shock	31 (20.9)	8 (27.6)	23 (19.3)	0.327
Treatment				
Surgery – n (%)	48 (32.4)	10 (34.5)	38 (31.9)	0.793
Duration of hospitalization (days) – median (IQR)	40 (26-54)	51 (36-59)	38 (25-52)	0.011

**comparison between patients with and without CNS embolization. CNS: central nervous system; IQR: interquartile range; HIV: human immunodeficiency virus; BCNIE: blood culture negative infective endocarditis.*

n=2). Nevertheless, only 34.5% (n = 51) performed head CT or MRI, so the true incidence of CNS embolization could be underestimated. Considering only patients with left-sided IE, the incidence of CNS embolization was 24.2% (n=29). The characterization of patients with a diagnosis of CNS embolization is also detailed in Table 1. These patients were predominantly male, with a median age of 65 years; 48.3% had previously known valvular disease, 10.3 % were intravenous drug users, and 6.9% had human immunodeficiency virus (HIV) infection. Native valve endocarditis was more common (69.0%, n = 20), while prosthetic valve endocarditis occurred in 31.0%, with 33.3% of prosthesis (n = 3) implanted in the preceding 12 months.

Among patients with HIV infection, 47.4% (n = 9) were treated with antiretroviral therapy, the median CD4 count was 202.5 cells/μl (interquartile range 10 – 402.5 cells/μl), 62.5% (n = 10) had undetectable viral load (median viral load of 0 copies/ml; interquartile range of 0 – 3,127 copies/ml), and 46.7% (n = 7) had criteria for acquired immunodeficiency syndrome (AIDS).

Patients with CNS embolization presented with ischemic stroke in 75.9% (n = 22) of cases (with hemorrhagic transformation in 27.3% of them; n = 6), hemorrhagic stroke in 17.2% (n = 5), mycotic aneurism in 17.2% (n = 5), and meningitis in 3.4% (n = 1). Upon admission, neurological symptoms were present in 41.4% (n = 12), and there were stroke recurrences (including both ischemic and hemorrhagic) in 34.5% (n=10) (Figure 1).

Predictors of CNS Embolization

Patients with CNS embolization, compared to those without it, were more likely to be younger than 75 years, to have diabetes, and to present without fever (Table 1). In addition, no patients with CNS embolization had involvement of right-sided valves, and they had longer hospitalization periods (median 51 *vs.* 38 days). There were no significant differences regarding the etiologic agent, the involvement of aortic or mitral valve, the proportion of patients submitted to surgery, or the outcome.

In multivariate logistic regression, the independent predictors of CNS embolization were diabetes and the absence of fever (hazard ratio – HR 3.78, and 2.41, respectively) (Table 2).

Outcomes in Patients with Neurological Complications

During follow-up (median 493 days, IQR 36-1,863), 34.5% of patients with CNS embolization (n = 10) were submitted to surgery. The median time from admission to surgery was 41 days (IQR 33-55) and from the diagnosis of the neurological complication to surgery was 36 days (IQR 28-43). Both in-hospital mortality and 1-year mortality were 39.3% (n=11) and all-cause mortality during follow-up was 46.4% (n=13) (Table 3).

Surgery was associated with reduced mortality, both in-hospital and at 1 year (mortality at 1 year in patients submitted to surgery: 0 *vs.* 57.9%; p=0.002). In addition to surgery, the other variables associated with in-hospital mortality were the occurrence of septic shock and invasive procedures in the preceding three months (Table 4). In multivariate Cox regression analysis, HIV infection was the only independent

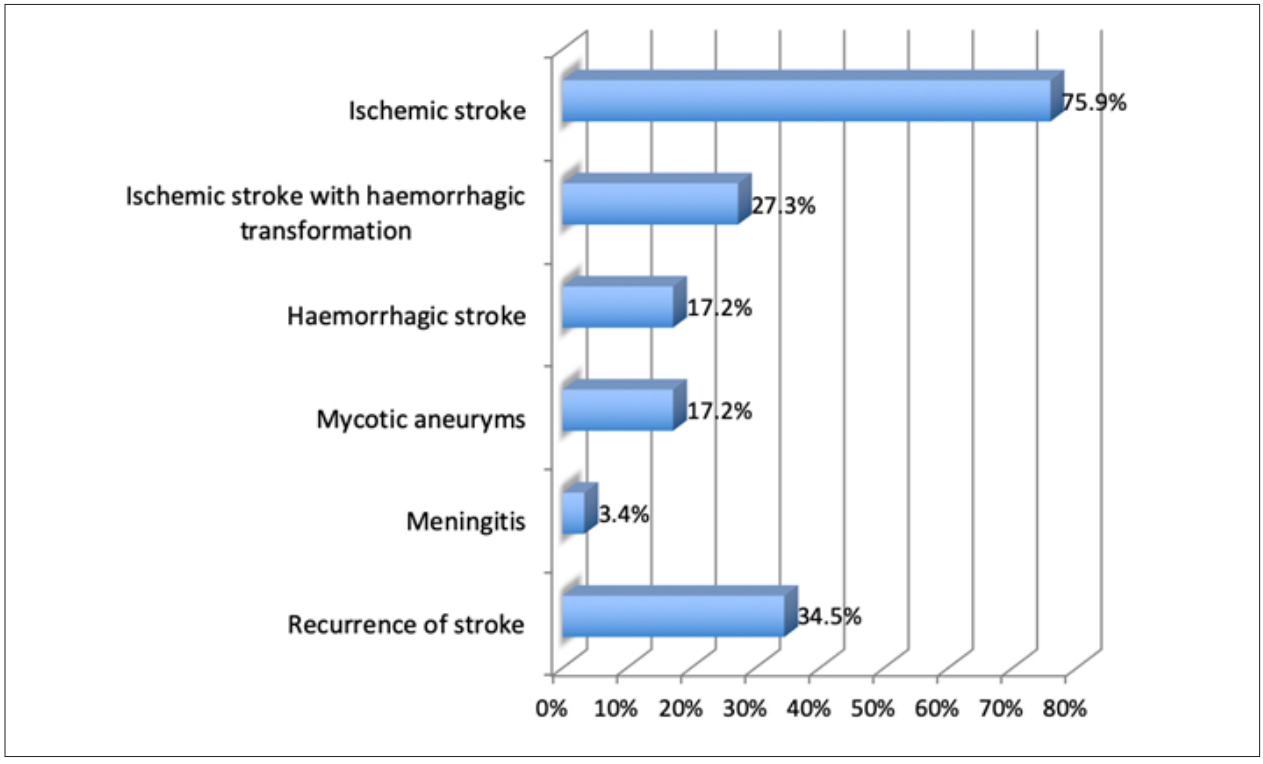


Figure 1 – *Neurological complications in patients with endocarditis (n=29).*

Table 2 – Predictors of central nervous system embolization

Characteristic	HR	95% CI	p
Diabetes mellitus	3.8	1.5-9.6	0.005
Absence of fever at presentation	2.4	1.0-5.8	0.049

HR: hazard ratio; CI: confidence interval.

Table 3 – Mortality of patients with endocarditis (n=142)

Characteristic – n (%)	Overall population (n=142)	Patients with CNS embolization (n=29)	Patients without CNS embolization (n=113)	p*
In-hospital mortality	43 (30.3)	11 (39.3)	32 (28.1)	0.247
One-year mortality	55 (38.7)	11 (39.3)	44 (38.6)	0.947
Overall mortality	64 (45.1)	13 (46.4)	51 (44.7)	0.872

**comparison between patients with and without CNS embolization. CNS: central nervous system.*

predictor of both in-hospital and one-year mortality (HR 10.5 and 10.6, respectively) (Tables 5 and 6, Figure 2).

Discussion

This retrospective observational study describes the incidence of neurological complications in a cohort of patients with IE from a single center during a 10-year period.

Neurological complications are a common and often predominant feature of IE[3,13,16-18] and the advent of CT and MRI enables a more reliable clinical assessment of these events. However, there are few available data about the risk of recurrent stroke, the best approach with regard to antithrombotic therapy, or the consequences of early surgery.[2]

The overall frequency of neurological complications in the present study cohort was around 20%, keeping up with the results from other large cohorts.[19,20] In the present study, it was also found that older patients had lower rates of these events, as previously reported,[19,21] although the cause of this reduction is not fully understood. Use of antiplatelet therapy[22,23] (often prescribed in aged patients), a hypothetical decline in hemostatic function, and smaller size of vegetations in this population are some of the reasons proposed,[17] but it is also possible that these events are simply underdiagnosed in this population due to mild clinical signs and symptoms.

Head imaging exams were not routinely performed in all patients, and the true incidence of ischemic complications is probably underestimated in the present cohort. Studies using MRI[6,24] have shown that acute brain embolizations are significantly more prevalent than it has been previously reported in studies based on clinical findings and CT scanning (30% of undetected events). With this taken into account, it is possible that some less symptomatic aged patients in the present study have been wrongly classified as having no neurological complications. However, other reports[20,25] have shown that small ischemic complications have no impact on the outcome of patients with IE, and, therefore, the essential conclusions would not be changed.

In the present study, the predictors of CNS embolization were a history of diabetes mellitus and the absence of fever at presentation. Several studies have shown mitral valve involvement and vegetation size to be important predictors of stroke,[10,17,19,26-29] whereas others have not confirmed this observation.[29-32] In the present cohort, mitral valve involvement was not associated with neurological complications. Vegetation size was not assessed, since measurements were not available for all patients and also due to a lack of standardization of the existing measurements. Some authors have emphasized the importance of vegetation size only when other factors are present, such as mitral valve location, and *Staphylococcus aureus* as the etiologic agent of IE.[30-33] In this cohort, it is possible to hypothesize that the influence of vegetation location and size on the development of embolic events was probably outweighed by factors that lead to a delay in the diagnosis and initiation of antibiotic therapy, such as the absence of fever at presentation. To our knowledge, diabetes mellitus has not previously been identified as a risk factor for CNS embolization in patients with IE, although it is associated with a worse prognosis in IE.[1] Nevertheless, diabetes is associated with an increased risk of cerebrovascular events and immunosuppression, so we can speculate that this condition may facilitate the growth of vegetations and increase the severity and clinical impact of embolization, when this complication occurs.

The timing of surgery in these patients is still a source of debate. Prompt surgery to prevent embolic events based on a vegetation size above 10 millimeters was proposed in early echocardiographic studies,[34] but higher rates of relapse and prosthesis dehiscence after surgery when antimicrobial treatment has not been completed remain a concern. In this regard, two recent studies have demonstrated that early surgery effectively decreases systemic embolism without increasing the IE relapse rate or prosthetic valve-related problems compared with the conventional treatment.[35,36]

Likewise, there is concern about the risk of postoperative neurological impairment when valve surgery is performed early after an ischemic or hemorrhagic episode, and the literature contains contradictory results. Some authors have found the risk of exacerbation to be low when surgery was performed within

Table 4 – Associations with in-hospital mortality in patients with central nervous system embolization

Characteristic	OR	95% CI	p
Diabetes *mellitus*	3.9	0.8-20.0	0.094
HIV infection	N/A	N/A	0.068
Invasive procedure in the preceding 3 months	4.5	0.7-27.7	0.096
Septic shock	9.0	1.4-59.8	0.014
Surgery	N/A	N/A	0.003

OR: odds ratio; CI: confidence interval; HIV: Human immunodeficiency virus; N/A: not applicable.

Table 5 – Independent predictors of in-hospital mortality in patients with central nervous system embolization

Characteristic	HR	95% CI	p
HIV infection	10.5	1.7-64.2	0.011

HR: hazard ratio, CI: confidence interval; HIV: human immunodeficiency virus.

Table 6 – Independent predictors of one-year mortality in patients with central nervous system embolization

Characteristic	HR	95% CI	p
HIV infection	10.6	1.7-64.8	0.011

HR: hazard ratio; CI: confidence interval; HIV: human immunodeficiency virus.

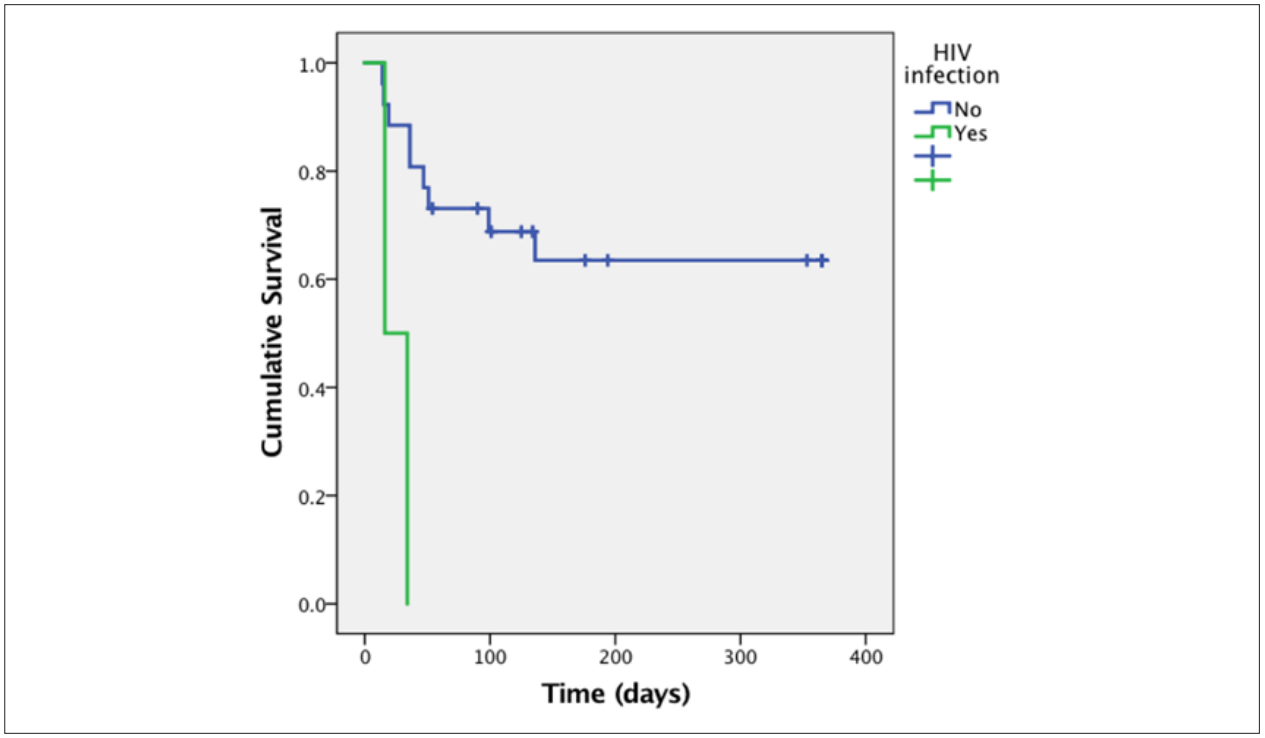


Figure 2 – *Kaplan-Meier survival curve of patients with endocarditis and neurological complications according to the status of human immunodeficiency virus infection. HIV: Human immunodeficiency virus.*

72 hours,[37] whereas others have reported that the risk is higher in early surgery and gradually decreases as the delay between the neurological event and the operation increases.[38] Considering the lack of controlled studies, recommendations are based on the results of published reports, and the generally accepted advice is to delay surgery for at least two weeks in the case of severe ischemic strokes and four weeks for hemorrhagic events.[38,39] The results of the study by García-Cabrera et al.[2] are in line with these recommendations, although the risk of postoperative complications was low after a small ischemic event, and therefore, minor events should not be an impediment to surgical valve repair when necessary.[2]

In our study, surgery was associated with reduced mortality, both in-hospital and at one year. However, this is a retrospective study and there was no matching between patients who were submitted to surgery or not, so we cannot conclude that surgery decreases mortality and can argue that these patients, selected by a multidisciplinary team, had a better prognosis and a more favorable risk profile compared to those not submitted to surgery. It should be emphasized that some patients with indication for surgery were probably considered too fragile or too unstable to undergo surgery, thus the results of the present study should be interpreted as suggesting that the improvement of prognosis is likely due to the careful selection of patients, and not to the presence of an indication for surgery, or to the performance of surgery *per se*.

Additionally, in our cohort, the median time to surgery since the diagnosis of neurological complications was 36 days, which is in line with most of the recommendations that point out that it should be appropriate to wait between two to four weeks, especially in extensive ischemic or hemorrhagic strokes.[1]

Contrary to most of the published literature, in our study, neurological complications were not associated with a significant increase in mortality, although in-hospital mortality was numerically higher in patients with neurological complications (39.3 *vs*. 28.1%, p=0.247).[13,19] We hypothesize that the association with mortality depends on the type and severity of neurological complications, although a standardized grading of the severity of cerebrovascular complications (clinical or radiological) is provided in very few reports.[20] For instance, in the study by García-Cabrera et al.[2] only moderate-to-severe ischemic events, particularly cerebral hemorrhages, were associated with a worse outcome, with hemorrhagic complications clearly related to *S. aureus* infection and anticoagulant therapy, which was mainly used in patients with mechanical prosthesis.[2]

In our cohort, in-hospital mortality was 30.3%, similar to published data ranging from 15 to 30%.[1] Prognosis in IE is influenced by patient characteristics, the presence or absence of cardiac and non-cardiac complications, the infecting organism and the echocardiographic findings, with patients with heart failure, periannular complications and/or *S. aureus* infection at highest risk.[1] To our knowledge, no published study reported the predictors of mortality in patients with IE and CNS embolization. In our study, the only predictor of both in-hospital and one-year mortality was HIV infection, which is often associated with involvement of the CNS, although it has not been associated with a worse prognosis in this population. Indeed, a study of 77 South African patients with endocarditis, 17 of which were HIV-infected, found a similar rate of complications in patients with and without HIV infection.[40]

Limitations

Due to the retrospective nature of this study, there are some limitations. First, as previously mentioned, head imaging exams were not routinely performed in all patients, which may result in an underestimation of the true incidence of embolic complications, since they are frequently clinically silent. Second, this was an observational study, with a relatively small sample, and some results should be interpreted with caution, namely the reduction in mortality in patients with neurological complications submitted to valve surgery, since more fragile patients or with more severe complications were probably less likely to be proposed or were refused surgery, resulting in selection bias.

On the other hand, this study assessed a cohort from an institution with a single surgical referral center, implying that the decisions regarding the performance and timing of surgery after the event were approximately the same.

Conclusions

In this population, embolization to the CNS was common, more often presented as ischemic stroke, and was associated with longer hospitalization, although there were no significant differences in mortality. This study is in line with recent data that showed that surgery should be the favored approach in patients with CNS embolization, after careful multidisciplinary selection. It also shows that patients with septic shock and HIV infection have a particularly poor prognosis, highlighting the role of the endocarditis team with a multidisciplinary approach.

Author contributions

Conception and design of the research and Acquisition of data: Alegria S, Marques A, Cruz I, Broa AL, Pereira ARF; Analysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Alegria S; Critical revision of the manuscript for intellectual content: Alegria S, Cruz I, João I, Simões O, Pereira H.

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 study was approved by the Ethics Committee of the Gabinete de Investigação do Centro Garcia de Orta under the protocol number 31/2017. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013

References

1. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Zotti F, et al. ESC Scientific Document Group. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36(44)3075-128.
2. García-Cabrera E, Fernández-Hidalgo N, Almirante B, Ivanova-Gerogieva R, Noureddine M, Plata A, et al. Neurological Complications of Infective Endocarditis: Risk Factors, Outcome, and Impact of Cardiac Surgery: A Multicenter Observational Study. Circulation, 2013;127(23):2272-84.
3. Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler VG, Bayer AS, et al. International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) Investigators. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med. 2009;169(5):463–73.
4. Snygg-Martin U, Gustafsson L, Rosengren L, Alsio A, Ackerholm P, Andersson R, et al. Cerebrovascular complications in patients with left-sided infective endocarditis are common: a prospective study using magnetic resonance imaging and neurochemical brain damage markers. Clin Infect Dis, 2008;47(1):23-30.
5. Duval X, Lung B, Klein I, Brochet E, Thabut G, Arnoult F, et al. Effect of early cerebral magnetic resonance imaging on clinical decisions in infective endocarditis: a prospective study. Ann Intern Med, 2010;152(8):497–504, W175.
6. Hess A, Klein I, Iung B, Lavallée P, Habensus E, Dornic Q, et al. Brain MRI findings in neurologically asymptomatic patients with infective endocarditis. AJNR Am J Neuroradiol, 2013;34(8):1579–84.
7. Novy E, Sonneville R, Mazighi M, Klein I, Mariotte E, Mourvillier B, et al. Neurological complications of infective endocarditis: New breakthroughs in diagnosis and management. Med Mal Infect. 2013; 43(11-12):443–50
8. Thuny F, Di Salvo G, Belliard O, Avierinos J, Pergola V, Rosenberg V, et al. Risk of embolism and death in infective endocarditis: prognostic value of echocardiography: a prospective echocardiographic study. Circulation. 2005;112(1):69–75.
9. Pruitt AA, Rubin RH, Karchmer AW, Duncan GW. Neurologic complications of bacterial endocarditis. Medicine (Baltimore). 1978;57(4):329–43.
10. Sonneville R, Mirabel M, Hajage D, Tubach F, Vignon P, Perez P, et al. Neurologic complications and outcomes of infective endocarditis in critically ill patients: the ENDOcardite en REAnimation prospective echocardiographic study. Crit Care Med. 2011;39(6):1474–81.
11. Vilacosta I, Graupner C, San Roman JA, Sarria C, Ronderos R, Ferandéz C, et al. Risk of embolization after institution of antibiotic therapy for infective endocarditis. J Am Coll Cardiol. 2002;39(9):1489–95.
12. Dickerman SA, Abrutyn E, Barsic B, Cecchi E, Moreno A, Doco-Lecompte T, et al. The relationship between the initiation of antimicrobial therapy and the incidence of stroke in infective endocarditis: an analysis from the ICE Prospective Cohort Study (ICE-PCS). Am Heart J. 2007;154(6):1086–94.
13. Heiro M, Nikoskelainen J, Engblom E, Kotilainen E, Marttila R, Kotilainen P. Neurologic manifestations of infective endocarditis: a 17-year experience in a teaching hospital in Finland. Arch Intern Med. 2000;160(18):2781–7.
14. Duval X, Delahaye F, Alla F, Tattevin P, Obadia J, Moing V, et al. Temporal trends in infective endocarditis in the context of prophylaxis guideline modifications: three successive population-based surveys. J Am Coll Cardiol. 2012;59(22):1968–76.
15. Derex L, Bonnefoy E, Delahaye F. Impact of stroke on therapeutic decision making in infective endocarditis. J Neurol. 2010;257(3):315–21.
16. Gálvez-Acebal J, Rodríguez-Baño J, Martínez-Marcos FJ, Reguera JM, Plata A, Ruiz J, et al. Grupo para el Estudio de las Infecciones Cardiovasculares de la Sociedad Andaluza de Enfermedades Infecciosas (SAEI). Prognostic factors in left-sided endocarditis: results from the Andalusian echocardiographic cohort. BMC Infect Dis. 2010;10:17.
17. Mangoni ED, Adinol LE, Tripodi MF, Andreana A, Gambardella M, Ragone E, et al. Risk factors for "major" embolic events in hospitalized patients with infective endocarditis. Am Heart J. 2003;146(2):311–6.
18. Heiro M, Helenius H, Hurme S, Savunen T, Engbom E, Nikoskelainen J, et al. Short-term and one-year outcome of infective endocarditis in adult patients treated in a Finnish teaching hospital during 1980-2004. BMC Infect Dis. 2007;7:78.
19. Cabell CH, Pond KK, Peterson GE, Durack DT, Corey GR, Anderson DJ, et al. The risk of stroke and death in patients with aortic and mitral valve endocarditis. Am Heart J. 2001;142(1):75–80.
20. Thuny F, Avierinos JF, Tribouilloy C, Giorgi R, Casalta J, Milandre L, et al. Impact of cerebrovascular complications on mortality and neurologic outcome during infective endocarditis: a prospective multicentre study. Eur Heart J. 2007;28(9):1155–61.
21. Durante-Mangoni E, Bradley S, Selton-Suty C, Tripodi M, Basic B, Bouza E, et al. International Collaboration on Endocarditis Prospective Cohort Study Group. Current features of infective endocarditis in elderly patients: results of the International Collaboration on Endocarditis Prospective Cohort Study. Arch Intern Med. 2008;168(19):2095–103.
22. Anavekar NS, Tleyjeh IM, Anavekar NS, Mirzoyev Z, Steckelberg JM, Haddad C, et al. Impact of prior antiplatelet therapy on risk of embolism in infective endocarditis. Clin Infect Dis. 2007;44(9):1180–6.
23. Chan KL, Dumesnil JG, Cujec B, Sanfilippo AJ, Jue J, Turek MA, et al. Investigators of the Multicenter Aspirin Study in Infective Endocarditis. A randomized trial of aspirin on the risk of embolic events in patients with infective endocarditis. J Am Coll Cardiol. 2003;42(5):775–80.
24. Cooper HA, Thompson EC, Laureno R, Fuisz A, Mark AS, Lin M, et al. Subclinical brain embolization in left-sided infective endocarditis: results from the Evaluation by MRI of the Brains of Patients With Left-Sided Intracardiac Solid Masses (EMBOLISM) pilot study. Circulation. 2009;120(7):585–91.
25. Ruttmann E, Willeit J, Ulmer H, Chevtchik O, Hofer D, Poewe W, et al. Neurological outcome of septic cardioembolic stroke after infective endocarditis. Stroke. 2006;37(8):2094–9.
26. Buda AJ, Zotz RJ, LeMire MS, Bach DS. Prognostic significance of vegetations detected by two-dimensional echocardiography in infective endocarditis. Am Heart J. 1986;112:1291–6.
27. Stafford WJ, Petch J, Radford DJ. Vegetations in infective endocarditis: clinical relevance and diagnosis by cross sectional echocardiography. Br Heart J. 1985;53(3):310–3.
28. Di Salvo G, Habib G, Pergola V, Avierinos JF, Philip E, Casalta JP, et al. Echocardiography predicts embolic events in infective endocarditis. J Am Coll Cardiol. 2001;37(4):1069–76.
29. Tischler MD, Vaitkus PT. The ability of vegetation size on echocardiography to predict clinical complications: a meta-analysis. J Am Soc Echocardiogr. 1997;10(5):562–8.
30. Hart RG, Foster JW, Luther MF, Kanter MC. Stroke in infective endocarditis. Stroke. 1990;21(5):695–700.
31. Salgado AV, Furlan AJ, Keys TF, Nichols TR, Beck GJ. Neurologic complications of endocarditis: a 12-year experience. Neurology. 1989;39(2 pt 1):173–8.
32. Steckelberg JM, Murphy JG, Ballard D, Bailey K, Tajik AJ, Taliercio CP, et al. Emboli in infective endocarditis: the prognostic value of echocardiography. Ann Intern Med. 1991;114(8):635–40.
33. Heinle S, Wilderman N, Harrison JK, Waugh R, Bashore T, Nicely LM, et al. Value of transthoracic echocardiography in predicting embolic events in active infective endocarditis: Duke Endocarditis Service. Am J Cardiol. 1994;74(8):799–801.

34. Mügge A, Daniel WG, Frank G, Lichtlen PR. Echocardiography in infective endocarditis: reassessment of prognostic implications of vegetation size determined by the transthoracic and the transesophageal approach. J Am Coll Cardiol. 1989;14(8):631–8.

35. Kim DH, Kang DH, Lee MZ, Yun SC, Kim YJ, Song MJ, et al. Impact of early surgery on embolic events in patients with infective endocarditis. Circulation. 2010;122(11 Suppl):S17–22.

36. Kang DH, Kim YJ, Kim SH, Sun BJ, Kim DH, Yun SC, et al. Early surgery versus conventional treatment for infective endocarditis. N Engl J Med. 2012;366(26):2466–73.

37. Piper C, Wiemer M, Schulte HD, Horstkotte. Stroke is not a contraindication for urgent valve replacement in acute infective endocarditis. J Heart Valve Dis. 2001;10(6):703–11.

38. Eishi K, Kawazoe K, Kuriyama Y, Kitoh Y, Kawashima Y, Omae T. Surgical management of infective endocarditis associated with cerebral complications: multi-center retrospective study in Japan. J Thorac Cardiovasc Surg. 1995;110(6):1745–55.

39. Angstwurm K, Borges AC, Halle E, Schielke E, Einhaulp KM, Weber JR. Timing the valve replacement in infective endocarditis involving the brain. J Neurol. 2004;251(10):1220–6.

40. Nel SH, Naidoo DP. An echocardiographic study of infective endocarditis, with special reference to patients with HIV. Cardiovasc J Afr. 2014;25(2):50-7.

Managing Patients with Infectious Endocarditis and Neurological Complication — The Big Dilemma that Persists Until these Days

Claudio Querido Fortes[1,2] *and Natália Rodrigues Querido Fortes*[1,3]

Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro,[1] *Rio de Janeiro, RJ - Brazil*

Faculdade de Medicina, Universidade Estácio de Sá,[2] *Rio de Janeiro, RJ - Brazil*

Hospital Universitário Antonio Pedro, Universidade Federal Fluminense,[3] *Niterói, RJ – Brazil*

Short Editorial related to the article: Neurological Complications in Patients with Infective Endocarditis: Insights from a Tertiary Centre

Endocarditis is an extremely challenging disease, both regarding diagnosis and due to the diversity of its presentation, as well as its management, which requires an endocarditis team including professionals from different specialties. An infectious disease specialist, clinical microbiologist, cardiologist, cardiac surgeon, neurologist and imaging specialist are of the essence, and assistance from other specialists is also desirable depending on each case. Its incidence has been increasing in recent decades, especially due to population aging, the growing number of individuals undergoing renal replacement therapy, the higher frequency of patients with prosthetic valves and cardiac electrical devices and also due to the technological advances in invasive diagnostic and therapeutic methods, in addition to the current "epidemic" of recreational intravenous drugs, which have become a serious public health problem in some countries. Despite all the progress made in the diagnosis and treatment of endocarditis, its mortality remains alarmingly high. The persistence of this high mortality may be partially explained by the increase in the number of older fragile patients with multiple comorbidities and patients with prostheses.

The main objectives of the article " Neurological Complications in Patients with Infective Endocarditis: Insights from a Tertiary Centre"[1] are to evaluate the predictors of neurological complications in patients with infective endocarditis, the predictors of mortality in this group, and to compare the results of clinical treatment with a general practitioner and a surgeon, both among the study population, and stratifying the group of patients with neurological complications.

In the Alegria et al.[1] cohort, the independent predisposing factors for the development of neurological complications were diabetes and the absence of fever at presentation. This is an interesting information, as diabetes is little cited as a predictive factor for cerebral embolization in patients with endocarditis, although it has been mentioned in the European Society of Cardiology (ESC)[2] and is one of the variables in the calculator developed by Hubert et al.,[3] to assess the risk of embolization in patients with endocarditis. The absence of fever on admission is not mentioned in the literature as being related to neurological complications. However, this is an intriguing finding, as it may be reflecting delayed diagnosis of endocarditis and, therefore, a longer time stretch until initiation of proper antibiotic therapy, increasing the chances of embolization to the central nervous system (CNS), since most neurological complications occur before hospitalization or during the first week of antibiotic therapy, significantly decreased after the second week of antimicrobial therapy. Another predictor of embolization mentioned by the authors was the patient's age, although it did not present statistical significance in the multivariate analysis. It is important to note that in most cohorts, including that of Alegria et al.,[1] older age is related to lower risk for cerebral embolization in patients with endocarditis.[4,5] However, in the calculator by Hubert et al.,[3] age over 70 is considered to be associated with an increased risk of embolization.

Interestingly, endocarditis involving the mitral valve and the infecting microorganism being *S. aureus*, predisposing factors for the development of neurological complications, classically described in most publications, were not found in this cohort.[4,6] The size of the vegetation, which is the main predisposing factor for embolization, was unfortunately not evaluated in this cohort, as the vegetation was not measured in all patients.

Alegria et al.[1] address one of the most distressing dilemmas that the endocarditis team may face: decision-making for patients with neurological abnormalities resulting from endocarditis and persisting vegetation with high embolic potential or a potentially fatal complication, whose cardiac surgery is the only possible treatment. The three main complications that require surgical treatment are hemodynamic deterioration, prevention of embolization or its recurrence, and persistent infection. The issue is not restricted to the decision to submit the patient to surgery or not, but also as to the ideal moment for the intervention.

When surgical indication is due to hemodynamic deterioration, even with all the risk of progression of neurological injury resulting from cardiopulmonary bypass (CPB), because a fatal outcome, without surgical intervention, is well known. The same occurs when surgical indication is persistence of infection. However, the greatest distress arises when indication for surgical treatment is to prevent the recurrence of embolization to the CNS, as, in this situation, in addition to the inherent risk of the surgical procedure (which

Keywords

Endocarditis, Bacterial/complications; Mortality; Neurologic, Complications; Renal Insufficiency; Heart Valve Prosthesis; Pandemics/complications; Aging; Embolization.

Mailing Address: Claudio Querido Fortes •
Universidade Federal do Rio de Janeiro - Serviço de Doenças Infecciosas e Parasitárias - 5o andar - Rua Rodolpho Paulo Rocco, 255 - Ilha do Fundão. Postal Code 21941-590, Rio de Janeiro, RJ – Brazil
E-mail: querido.fortes@gmail.com

DOI: https://doi.org/10.36660/abc.20210198

is also present when the indications for the procedure are hemodynamic deterioration and persistence of infection), there is still a potentially fatal risk of worsening the neurological condition. In this situation, even if surgery has been chosen, another very controversial point in the literature is the moment when it should be performed.

The authors report that the average time between diagnosis and surgery was 4 weeks (36 days) and that this would be the time interval required to avoid worsening the neurological complication as a result of the necessary heparinization for cardiopulmonary bypass, which is consistent with the current international guidelines.

The latest European guideline recommends postponing cardiac surgery for at least 4 weeks in the presence of intracranial hemorrhage to prevent heparinization during cardiopulmonary bypass from increasing bleeding area or to prevent the conversion of ischemic infarction to hemorrhagic infarction. Besides, the non-pulsatile flow of cardiopulmonary bypass and hypotension during surgery may impair cerebral circulation and promote extension of cerebral infarction area. The authors of the guideline consider that the potential damage that cardiopulmonary bypass may cause is greater than the benefit that surgery can bring, but these recommendations are based on expert opinion.

Over the last decade, several publications reported that the presence of asymptomatic neurological complications or transient ischemic attacks does not increase the risk of neurological complications in the postoperative period, and that, therefore, cardiac surgery can be performed at any time.[7] When the patient has a small cerebral infarction with little neurological repercussion, they recommend that cardiac surgery be performed after 1 to 2 weeks after the neurological event, and other articles recommended that the interval could be less than 7 days. Others considered that surgery should be performed within the first 72 hours after the onset of the neurological condition and that after this interval the possibility of complications would be greater.[8,9] However, the study by García-Cabrera et al.,[4] in 2013, is consistent with the systematic literature review carried out by Tam et al.,[10] where they concluded that patients with ischemic stroke can benefit from a delay of 1 to 2 weeks for surgery and those with a hemorrhagic event, more than 21 days.[4,10] However, the most recent publications continue to recommend shorter intervals.[11,12]

The greatest fears are severe neurological impairment or intracranial hemorrhage. In these situations, some researchers recommend not to operate the patient or to perform cardiac surgery after 1 month, in line with the current international guidelines. However, many recent publications have not found an association between the presence of cerebral hemorrhage or extensive infarction with significantly greater chances of neurological complications in the postoperative period,[5,12] but, as mentioned before, care should be taken in the interpretation of these results, because, even if the total population of patients evaluated by these authors is not small, after stratifications, the number of participants in each group to be analyzed ends up being too small, in addition to the possibility of selection bias. Presently, a significant number of authors continue to recommend an interval of at least 21 days between the hemorrhagic event and the surgery, unless a surgery delay puts the patient's life at risk.[12]

In the cohort of Alegria et al.,[1] operated patients had lower mortality compared to those treated exclusively with antimicrobials, which is in line with most of the current literature.[13] Alegria et al.[1] found no difference in the mortality of patients with or without neurological complications, which was different from most of the literature, as the authors themselves argued.[4,514]

When they compared the data after stratification of the group of patients with neurological complications who underwent the surgical procedure to the group of patients treated with antibiotic therapy only, they found lower mortality in the group undergoing the surgical procedure, which is in line with most of the latest publications,[5] but the authors call attention to the possibility of a selection bias.

Regarding the independent factors of mortality in patients with endocarditis with neurological complications, the authors found that only HIV infection was shown to be statistically significant, but this result may not be repeated in other cohorts, since only two patients had HIV infection and neurological complications from endocarditis.

In conclusion, despite the limitations mentioned by the authors, the cohort of Alegria et al.[1] presents extremely interesting results, such as diabetes as a predictive factor for embolization and HIV infection as independently related to mortality. It also presents, in a very detailed way, aspects related to surgical treatment in patients with endocarditis and neurological complications.

Finally, there are, to date, no data that allow the creation of more robust recommendations regarding the approach of patients with endocarditis who have developed a neurological complication. The guidelines can help, but the decision must be made by the endocarditis team considering the particular characteristics of each patient and each case.

References

1. Alegria A, Marques A, Cruz I, Broa AL, Pereira ARF, João I, et al. Complicações Neurológicas em Pacientes com Endocardite Infecciosa: Perspectivas de um Centro Terciário. Arq Bras Cardiol. 2021; 116(4):682-691.

2. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Zotti F, et al. ESC Guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36(44):3075-128.

3. Hubert S, Thuny F, Resseguier N, Giorgi R, Tribouilloy C, Dolley Y, et al. Prediction of symptomatic embolism in infective endocarditis: construction and validation of a risk calculator in a multicenter cohort. J Am Coll Cardiol. 2013;62(15):1384-92.

4. Garcia-Cabrera E, Fernandez-Hidalgo N, Almirante B, Ivanova-Georgieva R, Noureddine M, Plata A, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. Circulation. 2013;127(23):2272-84.

5. Diab M, Musleh R, Lehmann T, Sponholz C, Pletz MW, Franz M, et al. Risk of postoperative neurological exacerbation in patients with infective endocarditis and intracranial haemorrhage. Eur J Cardiothorac Surg. 2020 Oct 9;ezaa347. [Epub ahead of print].

6. Sotero FD, Rosario M, Fonseca AC, Ferro JM. Neurological complications of infective endocarditis. Curr Neurol Neurosci Rep. 2019;19(5):23.

7. Carneiro TS, Awtry E, Dobrilovic N, Fagan MA, Kimmel S, Weinstein ZM, et al. Neurological complications of endocarditis: a multidisciplinary review with focus on surgical decision making. Semin Neurol. 2019;39(4):495-506.

8. Bonaros N, Czerny M, Pfausler B, Müller S, Bartel T, Thielmann M, et al. Infective endocarditis and neurologic events: indications and timing for surgical interventions. Eur Heart J Suppl. 2020;22(Suppl M):M19-M25.

9. Ruttmann E, Willeit J, Ulmer H, Chevtchik O, Höfer D, Poewe W, et al. Neurological outcome of septic cardioembolic stroke after infective endocarditis. Stroke. 2006;37(8):2094-9.

10. Tam DY, Yanagawa B, Verma S, Ruel M, Fremes SE, Mazine A, et al. Early vs late surgery for patients with endocarditis and neurological injury: a systematic review and meta-analysis. Can J Cardiol. 2018;34(9):1185-99.

11. Zhang LQ, Cho SM, Rice CJ, Khoury J, Marquard RJ, Buletko AB, et al. Valve surgery for infective endocarditis complicated by stroke: surgical timing and perioperative neurological complications. Eur J Neurol. 2020;27(12):2430-8.

12. Ruttmann E, Abfalterer H, Wagner J, Grimm M, Müller L, Bates K, et al. Endocarditis-related stroke is not a contraindication for early cardiac surgery: an investigation among 440 patients with left-sided endocarditis. Eur J Cardiothorac Surg. 2020;58(6):1161-7.

13. Scheggi V, Alterini B, Olivotto I, Del Pace S, Zoppletti N, Tomberli B, et al. Embolic risk stratification and prognostic impact of early surgery in left-sided infective endocarditis. Eur J Intern Med. 2020 Aug;78:82-7.

14. Jawad K, Kroeg G, Koziarz A, Lehmann S, Dieterlen M, Feder S, et al. Surgical options in infective valve endocarditis with neurological complications. Ann Cardiothorac Surg. 2019;8(6):661-6.

Access to Reperfusion Therapy and Mortality in Women with ST-Segment–Elevation Myocardial Infarction: VICTIM Register

Jussiely Cunha Oliveira,[1,2] Mayse Pereira Souza Barros,[3] Ikaro Daniel de Carvalho Barreto,[4] Rubens Cruz Silva Filho,[3] Volfanio Araújo Andrade,[3] André de Melo Oliveira,[3] Ticiane Clair Remacre Munareto Lima,[1] Jeferson Cunha Oliveira,[1,5] Larissa Andreline Maia Arcelino,[1,6] Laís Costa Souza Oliveira,[1,5] Eduesley Santana-Santos,[2] Marcos Antônio Almeida-Santos,[7] Antônio Carlos Sousa,[1,3,8,9] José Augusto Soares Barreto-Filho[1,3,8]

Universidade Federal de Sergipe - Núcleo de Pós-Graduação em Ciências da Saúde,[1] São Cristóvão, SE - Brazil
Universidade Federal de Sergipe - Núcleo de Pós-graduação em Enfermagem,[2] São Cristóvão, SE - Brazil
Universidade Federal de Sergipe – Medicina,[3] São Cristóvão, SE - Brazil
Universidade Federal Rural de Pernambuco - Núcleo de Pós-graduação em biometria e estatística aplicada,[4] Recife, PE - Brazil
Hospital Primavera,[5] Aracaju, SE - Brazil
Hospital Universitário da Universidade Federal de Sergipe (HU-UFS),[6] Aracaju, SE - Brazil
Programa de Pós-graduação em Saúde e Ambiente da Universidade Tiradentes,[7] Aracaju, SE - Brazil
Fundação São Lucas - Centro de Ensino e Pesquisa,[8] Aracaju, SE - Brazil
Universidade Federal de Sergipe - Divisão de Cardiologia do Hospital Universitário,[9] São Cristóvão, SE - Brazil

Abstract

Background: **Myocardial reperfusion is a fundamental part of the treatment for ST elevation myocardial infarction (STEMI) and is responsible for reducing morbidity and mortality in affected patients. However, reperfusion rates are usually lower and mortality rates higher in women compared to men.**

Objectives: **To evaluate the prevalence of the use of reperfusion therapies among women and men with STEMI in hospitals where percutaneous coronary intervention (PCI) is available in the state of Sergipe.**

Methods: **This is a cross-sectional study that used data from the VICTIM Register. Patients diagnosed with STEMI admitted to the four hospitals (one public and three private) where PCI is available in the state of Sergipe were evaluated, from December 2014 to June 2018. A multivariate analysis with adjusted model using mortality as a dependent variable was made. In all analyses, the level of significance adopted was 5% ($p < 0.05$).**

Results: **A total of 878 volunteers with a confirmed diagnosis of STEMI, of which 33.4% were women, were included in the study. Only 53.3% of the patients underwent myocardial reperfusion (134 women versus 334 men). Fibrinolysis was performed only in 2.3% of all patients (1.7% of women versus 2.6% of men; $p = 0.422$). The rate of primary PCI was lower (44% versus 54.5%; $p = 0.003$) and hospital mortality was higher (16.1% versus 6.7%; $p < 0.001$) in women than in men.**

Conclusions: **Women have significantly lower rates of primary PCI and higher hospital mortality. Reperfusion rates were low in both sexes and there was a clear underutilization of thrombolytic agents. (Arq Bras Cardiol. 2021; 116(4):695-703)**

Keywords: **Myocardial Infarction; Women; Myocardial Reperfusion; Percutaneous Coronary Intervention; Morbimortality; Gender and Health; Healthcare Disparities**

Introduction

Early myocardial reperfusion is the mainstay of the treatment of acute myocardial infarction with ST elevation (STEMI) and its use is associated with better prognosis.[1] However, in different parts of the world, women have presented lower reperfusion rates than men.[2-6]

Percutaneous coronary intervention (PCI) is currently considered the gold standard treatment for STEMI because it has better success rates, a higher frequency of complete reperfusion (TIMI grade 3) and a lower incidence of recurrent ischemia, reinfarction and death when compared to fibrinolysis. The procedure is indicated for patients with STEMI who may have access to therapy within 90 minutes of diagnosis, in addition to those who have contraindications to the use of fibrinolytic drugs or in cardiogenic shock. Its use is beneficial if performed within 12 hours of the onset of pain, or up to 24 hours after diagnosis, if ischemia persists. The use of fibrinolytic drugs is of fundamental importance for patients who will not have timely access to PCI and patients in the prehospital environment.[1,7,8]

Despite the proven relevance of early coronary reperfusion therapy, several studies have shown disparities between sexes

Mailing Address: Jussiely Cunha Oliveira •
Universidade Federal de Sergipe - Cidade Univ. Prof. José Aloísio de Campos Av. Marechal Rondon, s/n. Postal Code 49100-000, Jd. Rosa Elze, São Cristóvão, SE – Brazil
E-mail: HYPERLINK "mailto:jussiely@hotmail.com" jussiely@hotmail.com
Manuscript received July 15, 2019, revised mnauscript January 23, 2020, accepted March 16, 2020

DOI: https://doi.org/10.36660/abc.20190468

when it comes to the approach for patients with STEMI.[2-6] Women have lower rates of PCI and fibrinolysis than men[2-6] as well as more complications associated with reperfusion therapy.[9-11] In women, the prognosis after ischemia is worse than in men, possibly reflecting a less aggressive therapeutic approach.[4,6,12,13]

This study aimed to assess the prevalence of the use of reperfusion therapies among women and men with STEMI in hospitals where PCI is available in the state of Sergipe.

Materials and methods

This is a cross-sectional study that used data from the VICTIM Register[14] - Via Crucis for Treatment of Myocardial Infarction, collected from December 2014 to June 2018, in the four hospitals in Sergipe where PCI is available. All institutions are located in the capital; only one of them serves public service users and is renowned for its performance in the treatment of STEMI. The other institutions are private and offer assistance on demand.

The collection was carried out by the researchers using their own research questionnaire which was composed of the following variables: age, ethnicity, social class, education, health coverage, risk factors, symptoms at presentation, Killip and Kimball classification, GRACE risk score; data regarding the time elapsed between the onset of symptoms and the decision to call for help, the decision to call for help to arrival at the first hospital without angioplasty, time from the first hospital to the hospital with angioplasty, and the total time elapsed since the onset of symptoms until arrival at the hospital with angioplasty; use of fibrinolytic treatments, PCI or coronary artery bypass grafting, in addition to clinical course of patients during hospitalization after AMI regarding mortality, chronic heart failure, re-infarction, or shock. The information was collected through interviews with the patient or caregiver and from patients' medical records.

The study included all patients over 18 years of age admitted to the above-mentioned hospitals after confirmation of STEMI by an electrocardiogram, and according to the V Brazilian Society of Cardiology guidelines,[1] which suggests the presence of at least one of the following five criteria for confirmation of the diagnosis of infarction: symptoms of myocardial ischemia such as chest pain; changes in the ST segment/T wave or complete left bundle branch block; development of pathological Q waves on the ECG; imaging evidence of loss of viable myocardium or wall motion abnormalities; or the identification of an intracoronary thrombus by angiography or autopsy. In addition, patients signed an informed consent form before inclusion in the study.

Patients who died before the interview, patients who were not eligible for inclusion in the Via Crucis, that is, who were hospitalized for other causes when STEMI was detected and hence did not go through the timeline from the onset of out-of-hospital symptoms until arrival at the hospital with PCI; patients who did not sign the informed consent form; who suffered reinfarction within 28 days after the incident myocardial infarction; patients who had a change in diagnosis, that is, those who were admitted for STEMI, but were identified with another problem after the exams; and patients assisted by a health plan seen in a philanthropic hospital (Figure 1) were excluded from the study.

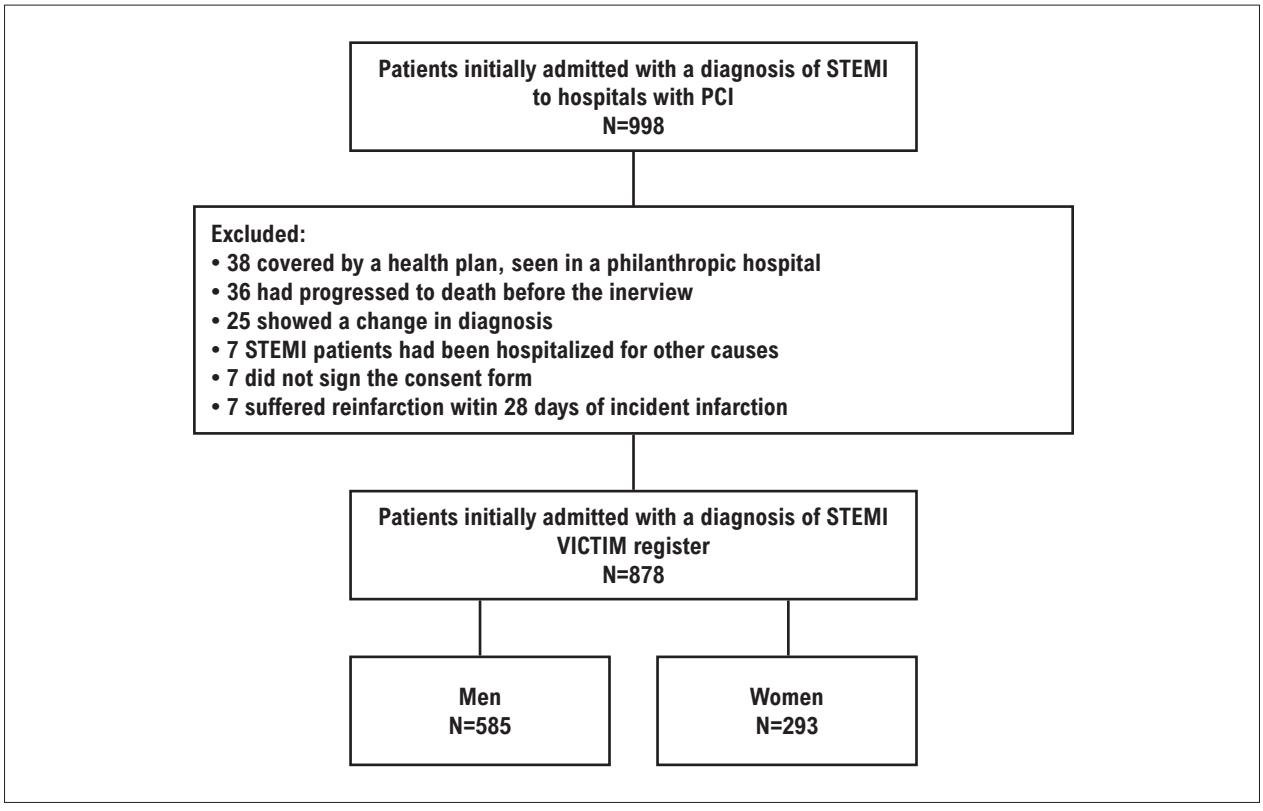


Figure 1 – *Flowchart of excluded patients; STEMI: ST elevation myocardial infarction.*

Data collection was carried out consecutively in the selected institutions.

This research was approved by research ethics committee of the Federal University of Sergipe (UFS) (approval number 483,749).

Statistical analysis

Categorical variables were described using absolute and relative frequency, and continuous variables were described using mean and standard deviation or median and interquartile range, according to the normality of the data. To assess differences in measures of central tendency, the Shapiro-Wilk test was first applied to assess the adherence of continuous variables to the normal distribution, and when the validity of this assumption was confirmed, the Student's t test was used for independent samples; otherwise, the Mann-Whitney test was used. Categorical variables were assessed using Pearson's χ^2 test. In the multivariate analysis, a simple logistic regression was used; mortality was the outcome and sex was the independent variable. The model was adjusted for health coverage, age, reperfusion and GRACE Risk Score. The statistical analysis was performed using the SPSS software for Windows version 17; results were considered statistically significant if p-values were less than 0.05, with 95% confidence interval.

Results

A total of 878 patients (33.4% women) diagnosed with STEMI were studied. Compared to men, women were older, most belonged to lower social class, did not finish college, and 30% never went to school. The predominant ethnic group was non-white in both groups and the most used service was the public service, as can be seen in Table 1.

Regarding the time from symptom onset to arrival at the hospital where PCI was available, no significant difference between sexes was observed in the time spent from the onset of symptoms to the decision to call for medical help, or in the time between the decision to call medical help and arrival at the first hospital without capacity to perform PCI. However, the time spent from presentation at the first hospital to arrival at the hospital where PCI was available was significantly longer for women than men, with a median of 460 h (IQ 233.75-1283.25) and 390 h (IQ 215- 775), respectively. The same was observed when only users of the Unified Health System (SUS) were analyzed, with a median of 535h (IQ 330-1565) and 450h (IQ 300-1035) for women and men, respectively. As for the total time spent between the onset of symptoms and arrival at the hospital where PCI was available, there was a significant delay to treatment in both men [545h (IQ332-1122)] and women 705h [(IQ 71-1612.5)]. This was clearly associated with the type of health system, as the time was longer for users of the public system compared with users of the private one [792.5h (456.75-1800) and 598h (390-1331.75), respectively]. In addition, in the public service, the number of women who were not reperfused was significantly greater than in the private service. No differences were found in the use of fibrinolytic agents, success of PCI, and coronary artery bypass grafting between men and women (Table 2).

However, the logistic regression between mortality and sex revealed a higher likelihood of death in the female sex [CR = 2.54 (95% CI: 1.58-4.06); $p < 0.001$], as well as when adjusted for health coverage [CR = 2.47 (95% CI: 1.54-3.96); $p < 0.001$], health coverage and age [CR = 2.27 (95% CI: 1.40-3.59); $p = 0.001$], health coverage, age and reperfusion [CR = 2.20 (95% CI: 1.35-3.59); $p = 0.002$], health coverage, age, reperfusion and GRACE risk score [CR = 2.36 (95% CI: 1.44-3.88); $p = 0.001$].

Discussion

In the present study, lower reperfusion rates and higher mortality rates were observed in women than in men. Moreover, the rate of use of reperfusion therapy was low in both sexes, and significantly lower in women. Several national and international studies have called attention to the low rates of reperfusion as a growing problem, and thus more effective strategies for the implementation of care protocols for the treatment of STEMI are urgently required.[15,16]

The present findings are similar to those of previous studies carried out in the north and northeast of Brazil reporting a reperfusion rate in patients with STEMI of 52.5%.[16] This confirms that we are far from meeting the recommendations on reperfusion rates, such as observed in developed countries. For example, the STRategical Reperfusion Early After Myocardial infarction (STREAM) study observed rates as high as 98.2% of patients treated and receiving some reperfusion strategy (thrombolysis with or without rescue or primary PCI) in a developed country.[17]

The present study also revealed an inequality between sexes, with lower rates of reperfusion in women when compared to men, especially when analyzing data from SUS users. Such inequality was also verified in several national and international studies,[2,3,4,6,18] such as the study conducted in China – Insights From the China Patient-Centered Evaluated Assessment the Cardiac Events (PEACE) – in which Chinese women had lower reperfusion rates even when they were promptly referred for treatment.[6] The study entitled Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) found that, in the United States, women were 2.31 times more likely to not receive reperfusion than men.[18]

Some studies have pointed out that the greater number of comorbidities and the fact of having a more severe condition at the time of the diagnosis of STEMI could expose women to the risk-treatment paradox, in which it is observed that patients with a more severe condition receive less therapeutic interventions.[19,20] In these cases, the physician may not offer adequate treatment because he believes that the intervention will be useless in view of the patient's severe state, or because he fears that the adverse effects will outweigh the benefits generated by the intervention in the patient with multiple comorbidities.[19] In the PEACE study, women had a higher frequency of risk factors than men, including those assessed in the present study, except smoking, which was more prevalent among men.[6] From this perspective, the Global Registry of Acute Coronary Events study found that women were older and had more comorbidities when treated with PCI.[20] Accordingly, in the present study, women were older, and had a higher number of associated risk factors and a more severe Killip and Kimball classification than men.

Table 1 – Demographic and clinical characteristics of patients with ST elevation myocardial infarction (STEMI)

Demography	Total (N = 878)	Men (N = 585)	Women (N = 293)	p value**	Public		p value**	Private		p value**
					Men (N = 474)	Women (N = 250)		Men (N = 111)	Women (N = 43)	
Age, years (mean ± SD)	61.8±12.2	61.0±11.9	63.4±12.8	0.004	61.1±12.0	62.5±12.7	0.115	60.5±11.5	68.8±12.2	<0.001
Ethnicity, n (%)										
White	311 (36.2)	204 (35.7)	107 (37.4)	0.616	137 (29.5)	84 (34.6)	0.170	67 (62.0)	23 (53.5)	0.334
Non-white	547 (63.8)	368 (64.3)	179 (62.6)		327 (70.5)	159 (65.4)		41 (38.0)	20 (46.5)	
Social class*, n (%)										
A + B	59 (7.2)	49 (8.9)	10 (3.7)	<0.001	7 (1.6)	3 (1.3)	0.006	42 (39.3)	7 (17.9)	0.049
C + D	342 (41.6)	245 (44.5)	97 (35.7)		188 (42.4)	70 (30.0)		57 (53.3)	27 (69.2)	
E	412 (51.2)	256 (46.5)	165 (60.7)		248 (56.0)	160 (68.7)		8 (7.5)	5 (12.8)	
Schooling, n (%)										
Never went to school	217 (24.7)	129 (22.1)	88 (30.0)	0.012	125 (26.4)	83 (33.2)	0.119	4 (3.6)	5 (11.6)	0.034
Primary to secondary school	581 (66.2)	395 (67.5)	186 (63.5)		337 (71.1)	159 (63.6)		58 (52.3)	27 (62.8)	
Higher education	80 (9.1)	61 (10.4)	19 (6.5)		12 (2.5)	8 (3.2)		49 (44.1)	11 (25.6)	
Health coverage, n (%)										
Public	724 (82.5)	474 (81.0)	250 (85.3)	0.114						
Private	154 (17.5)	111 (19.0)	43 (14.7)							
Risk factors, n (%)										
Diabetes mellitus	2909 (33.0)	167 (28.5)	123 (42.0)	<0.001	133 (28.1)	103 (41.2)	<0.001	34 (30.6)	20 (46.5)	0.064
Systemic arterial hypertension	565 (64.4)	345 (59.0)	220 (75.1)	<0.001	271 (57.2)	183 (73.2)	<0.001	74 (66.7)	37 (86.0)	0.016
Dyslipidemia	342 (39.0)	195 (33.3)	147 (50.2)	<0.001	139 (29.3)	120 (48.0)	<0.001	56 (50.5)	27 (62.8)	0.168
Smoking	271 (30.9)	184 (31.5)	87 (29.7)	0.594	172 (36.3)	82 (32.8)	0.350	12 (10.8)	5 (11.6)	0.885
Number of risk factors, n (%)										
0	105 (12.0)	86 (14.7)	19 (6.5)	<0.001	70 (14.8)	17 (6.8)	<0.001	16 (14.4)	2 (4.7)	0.018
1	277 (31.5)	208 (35.6)	69 (23.5)		173 (36.5)	63 (25.2)		35 (31.5)	6 (14.0)	
2	320 (36.4)	202 (34.5)	118 (40.3)		162 (34.2)	96 (38.4)		40 (36.0)	22 (51.2)	
3 or more	176 (20.0)	89 (15.2)	87 (29.7)		69 (14.6)	74 (29.6)		20 (18.0)	13 (30.2)	
Presentation symptoms, n (%)										
Typical pain	766 (87.2)	515 (88.0)	251 (85.7)	0.321	423 (89.2)	220 (88.0)	0.615	92 (82.9)	31 (72.1)	0.134
Atypical pain	81 (9.2)	52 (8.9)	29 (9.9)	0.626	38 (8.0)	23 (9.2)	0.586	14 (12.6)	6 (14.0)	0.824
KILLIP AND KIMBALL CLASSIFICATION, n (%)										
I	735 (84.5)	505 (86.9)	230 (79.6)	0.018	407 (86.0)	198 (80.2)	0.129	98 (90.7)	32 (76.2)	0.066
II	102 (11.7)	57 (9.8)	45 (15.6)		52 (11.0)	38 (15.4)		5 (4.6)	7 (16.7)	
III	19 (2.2)	9 (1.5)	10 (3.5)		7 (1.5)	8 (3.2)		2 (1.9)	2 (4.8)	
IV	14 (1.6)	10 (1.7)	4 (1.4)		7 (1.5)	3 (1.2)		3 (2.8)	1 (2.4)	
GRACE RISK SCORE, n (%)										
≤ 140 (low risk)	400 (48.3)	269 (49.0)	131 (47.0)	0.578	223 (50.6)	155 (48.3)	0.576	46 (42.6)	16 (39.0)	0.693
> 140 (high risk	428 (51.7)	280 (51.0)	148 (53.0)		218 (49.4)	123 (51.7)		62 (57.4)	25 (61.0)	

** Social class (IBGE) - A: > 20 minimum wages, B: 10-20 minimum wages, C: 4-10 minimum wages, D: 2-4 minimum wages, E: ≤ 2 minimum wages. ** men vs. women.*

Table 2 – Access to the angioplasty service, treatment and hospital outcomes of patients with ST elevation myocardial infarction (STEMI)

Timeline	Total (N = 878)	Men (N = 585)	Women (N = 293)	p value**	Public		p value**	Private		p value**
					Men (N = 474)	Women (N = 250)		Men (N = 111)	Women (N = 43)	
Time from symptom onset to decision to call for help, h (median, IIQ)	30 (13.75-150)	30 (15-160)	30 (10-150)	0.747	30 (15-150)	30 (10-131.25)	0.705	60 (15-210)	50 (15-180)	0.846
Time from decision to call for help to arrival at the first hospital, h (median, IIQ)	30 (15-60)	30 (15-60)	30 (15-60)	0.535	30 (20-60)	30 (19-60)	0.611	10 (0-30)	0 (0-16.25)	0.075
Time from arrival at the first hospital to arrival at the hospital with angioplasty service, h (median, IIQ)	412 (225-940)	390 (215-775)	460 (233.75-1283.25)	0.024	450 (300-1035)	535 (330-1565)	0.024	60 (30-200)	60 (30-135)	0.524
Time from symptom onset to arrival at the hospital with angioplasty, h (median, IIQ)	574.5 (347.75-1292.5)	545 (332-1122)	705 (371-1612.5)	0.005	598 (390-1331.75)	792.5 (456.75-1800)	0.003	221 (60-550)	150 (80-414)	0.939
Treatment										
Fibrinolytic agent, n (%)	20 (2.3)	15 (2.6)	5 (1.7)	0.422	14 (3.0)	4 (1.6)	0.266	1 (0.9)	1 (2.3)	0.484
Primary PCI *, n (%)	448 (51.0)	319 (54.5)	129 (44.0)	0.003	234 (49.4)	95 (38.0)	0.003	85 (76.6)	34 (79.1)	0.740
Success	321 (92.8)	226 (92.6)	95 (93.1)	0.866	153 (91.1)	67 (91.8)	0.858	73 (96.1)	28 (96.6)	0.905
Coronary artery bypass grafting, n (%)	29 (3.3)	20 (3.4)	9 (3.1)	0.786	14 (3.0)	7 (2.8)	0.907	6 (5.4)	2 (4.7)	0.850
Not reperfused, n (%) †	410 (46.7)	251 (42.9)	159 (54.3)	0.001	226 (47.7)	151 (60.4)	0.001	25 (22.5)	8 (18.6)	0.595
Hospital outcome										
Mortality, n (%)	86 (9.8)	39 (6.7)	47 (16.1)	<0.001	37 (7.8)	42 (16.9)	<0.001	2 (1.8)	5 (11.6)	0.009
CHF, n (%)	110 (12.5)	60 (10.3)	50 (17.1)	0.004	51 (10.8)	42 (16.9)	0.020	9 (8.1)	8 (18.6)	0.062
Reinfarction, n (%)	17 (1.9)	10 (1.7)	7 (2.4)	0.486	9 (1.9)	5 (2.0)	0.919	1 (0.9)	2 (4.7)	0.131
Shock, n (%)	46 (5.2)	27 (4.6)	19 (6.5)	0.236	19 (4.0)	16 (6.4)	0.150	8 (7.2)	3 (7.0)	0.960

** PCI: Percutaneous Coronary Intervention. † Not reperfused - those who did not use fibrinolytic agent and primary PCI. IIQ - Interquartile Interval; CHF: chronic heart failure; ** men vs. women*

As for the average time spent between arrival at the first hospital and access to the hospital with PCI service, a much longer time than that suggested by the Brazilian guideline[1] was observed when analyzing the total population. Analysis of the average time from symptom onset to arrival at the hospital with hemodynamics, stratified by sex, treatment delay was even greater among women, which was maintained in the analysis of SUS users only. Thus, the delay to arrive at the hospital with angioplasty reflected in low rates of use of primary PCI in the general population, with lower rates in women when compared with men in the general population (Figure 2) and among SUS users. In the evaluation of users of private health services, more expressive values were observed for the performance of primary PCI in females. In Brazil, factors associated with health service, such as difficult access and little structure, besides the inadequate choice of transportation made by patients, can contribute to inadequate access to therapy, leading to long delays.[15,21] Contrary to other reports,[12,22,23] in the present study, women did not experience significant delays, compared to men, when making a decision to call for help.

Values found for the use of fibrinolytic agents were lower than those observed in the PEACE study, which found that in 2011, 26.8% of women and 33.5% of men with STEMI were submitted to fibrinolysis.[6] Furthermore, the study entitled Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO I) reported a higher rate of mortality and complications among women after fibrinolysis when compared with the volunteers submitted to PCI,[11,24] since the early thrombolytic therapy, with due indication, reduces mortality in both sexes.[7] However, there are several barriers to the use of this therapy, since women have more contraindications to this method and greater risks of complications.[11]

In an American study conducted in 2018, mortality within 30 days after STEMI was 10.7% in women and 4.6% in men ($p = 0.002$).[25] In the present study, women had significantly higher rates of hospital mortality and post-ischemic heart failure than men. The GUSTO I[24] and ACC-NCDR[9] (National Cardiovascular Data Registry- American College of Cardiology) records corroborate the information and show that women are more likely to develop heart failure following AMI. However, the association of risk factors, greater delay in reach the hospital with PCI service, and age of appearance of the condition may also have impacted the higher mortality rate,[11,13] in addition to the longer time spent receiving treatment[9,14,15,26] and less access to adequate treatment.[4,6,12,13,15]

The present study brought an assessment between public and private services, which revealed worse results for users of the public service, especially among women. In addition, our findings point to an absence of public policies regarding adequate access of patients with STEMI to adequate treatment.

Limitations

The present study has some limitations that include the low social and educational level of participants, especially among SUS users, which may have compromised the self-reporting of their medical history. The collection of data on door-to-balloon time was compromised by the lack of information of times in the medical records, especially in the public service. In addition, only mortality and hospital outcomes were studied and there was no follow-up after discharge to assess whether there were disparities between sexes regarding prognosis after hospitalization.

Conclusion

Disparities between sexes were observed in the present study with lower rates of primary PCI and higher rates of hospital mortality among women. The low use of primary PCI was probably one of the variables responsible for the higher mortality in women. The low rates of reperfusion in women, both considering the general population and in SUS users only, were directly associated with delayed arrival at the hospital with hemodynamic service, since early reperfusion is the key point of treatment. Such findings point to the need for strategies to improve access of women with STEMI to effective therapeutic strategies.

Author contributions

Conception and design of the research: Oliveira JC, Barros MPS, Oliveira JC, Arcelino LAM, Barreto-Filho JAS; Almeida-Santos MA. Acquisition of data: Oliveira JC, Barros MPS, Silva Filho RC, Andrade VA, Oliveira AM, Lima TCRM, Oliveira JC, Arcelino LAM, Oliveira LCS; Analysis and interpretation of the data: Oliveira JC, Barros MPS, Barreto IDC, Oliveira AM, Lima TCRM, Oliveira JC, Arcelino LAM, Sousa AC, Barreto-Filho JAS; Almeida-Santos MA. Statistical analysis: Barreto IDC, Santana-Santos E, Barreto-Filho JAS; Almeida-Santos MA. Obtaining financing: Oliveira JC, Oliveira LCS, Barreto-Filho JAS; Almeida-Santos MA. Writing of the manuscript: Oliveira JC, Barros MPS, Barreto IDC, Silva Filho RC, Oliveira AM, Lima TCRM, Barreto-Filho JAS; Almeida-Santos MA. Critical revision of the manuscript for intellectual content: Barros MPS, Barreto IDC, Silva Filho RC, Andrade VA, Oliveira AM, Lima TCRM, Oliveira JC, Arcelino LAM, Oliveira LCS, Santana-Santos E, Sousa AC, Barreto-Filho JAS.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by CNPq, number 14/2013.

Study Association

This article is part of the thesis of Doctoral submitted by Jussiely Cunha Oliveira, from Universidade Federal de Sergipe.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Sergipe under the protocol number 483.749. 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.

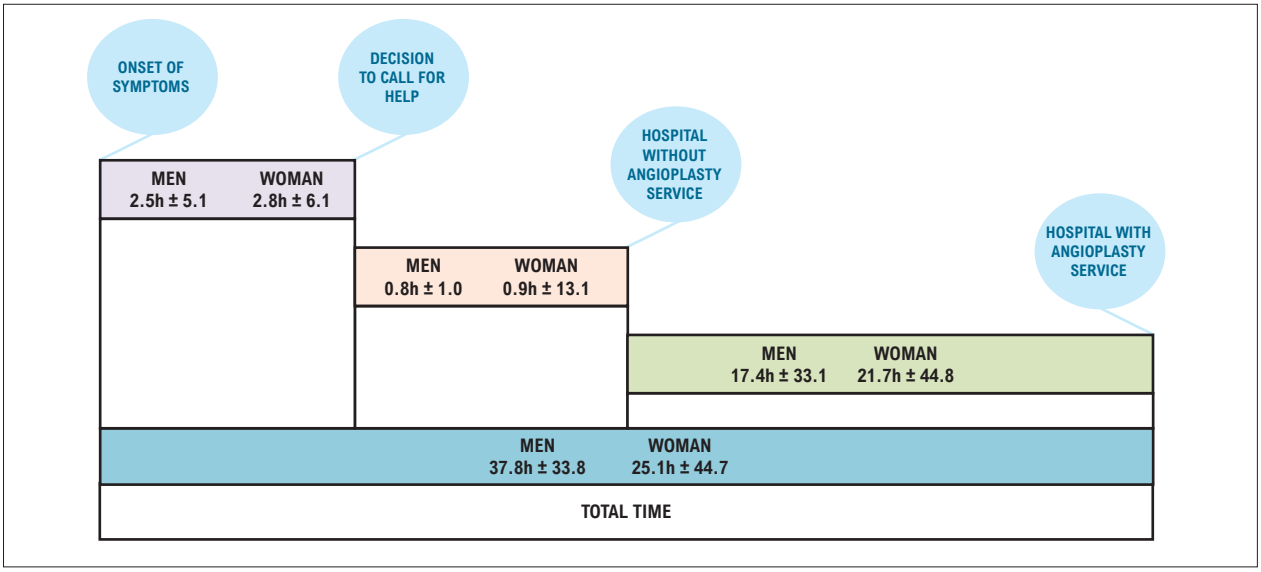


Figure 2 – *Timeline of access to treatment of patients with ST elevation myocardial infarction.*

References

1. Piegas LS, Timerman A, Feitosa GS, Nicolau JC,Mattos LAP, Andrade MD, et al.,Sociedade Brasileira de Cardiologia. V Diretriz da Sociedade Brasileira de Cardiologia sobre Tratamento do Infarto Agudo do Miocárdio com Supradesnível do Segmento ST. Arq Bras Cardiol. 2015; 105(2):1-105.
2. Radovanovic D, Erne P, Urban P, Bertel O, Rickli H, Gaspoz JM. Gender differences in management and outcomes in patients with acute coronary syndromes: results on 20 290 patients from the AMIS Plus Registry. Heart. 2007;93(11):1369–75.
3. Chieffo A, Hoye A, Mauri F, Mikhail G, Ammerer M, Grines C, et al. Gender-based issues in interventional cardiology: a consensus statement from the Women in Innovations (WIN) Initiative. Rev Esp Cardiol. 2010;63(2):200-8.
4. Gasperi R, Cantarelli MJ, Castello Jr HJ, Gonçalves R, Gioppato S, Guimarães JB, et al. Impacto do Sexo Feminino nos Resultados da Intervenção Coronária Percutânea Contemporânea. Rev Bras Cardiol Invasiva. 2011; 19(2): 178-183.
5. Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, et al. Heart disease and stroke statistics – 2011 update: a report from the American Heart Association. Circulation. 2011;123(4):e18-e209.
6. Du X, Spatz ES, Dreyer RP, Hu S, Wu C, Li S, et al. Sex differences in Clinical Profiles and Quality of Care Among Patients With ST-Segment Elevation Myocardial Infarction From 2001 to 2011: Insights From the China Patient-Centered Evalueted Assessment os Cardiac Events (PEACE): Retrospective Study. J Am Heart Assoc. 2016; 5(2):e002157
7. O'Gara PT, Kushner FG, Ascheim DD, Casey Jr DE, Chung MK, Lemos JA, et al. 2013 ACCF/AHA Guideline for the Management of ST Elevation Myocardial Infarction: A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2012;127(4):362-425.
8. Ibanez B, James S, Agewall S, Antunes MJ, Ducci CB, Bueno H, et al. Task Force on the management of ST-segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J. 2017;00:1–66.
9. Akhter N, Milford-Beland S, Roe MT, Piana RN, Kao J, Shroff A. Gender differences among patients with acute coronary syndromes undergoing percutaneous coronary intervention in the American College of Cardiology–National Cardiovascular Data Registry (ACC NCDR). Am Heart J. 2009;157(1): 141–148.
10. Yu J, Mehran R, Grinfeld L, Xu K, Nikolsky E, Brodie BR, et al. Sex-based differences in bleeding and long term adverse events after percutaneous coronary intervention for acute myocardial infarction: three year results from the HORIZONS-AMI trial. Catheter Cardiovasc Interv. 2015; 85(3):359-68.
11. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, et al. Acute Myocardial Infarction in Women: A Scientific Statement From the American Heart Association. Circulation. 2016; 133(9): 916-47.
12. Leurent G, Garlantezec R, Auffret V, Hacot JP, Coudert I, Filippi, et al. Gender differences in presentation, management and inhospital outcome in patients with STsegment elevation myocardial infarction: data from 5000 patients included in the ORBI prospective French regional registry. Arch Cardiovasc Dis. 2014; 107(5)291–298.
13. Freisinger E, Sehner S, Malyar NM, Suling A, Reinecke H, Wegscheider K. Nationwide Routine-Data Analysis of Sex Differences in Outcome of Acute Myocardial Infarction. Clin Cardiol. 2018 Aug;41(8):1013-21.
14. Oliveira JC, Oliveira LC, Oliveira JC, Barreto ID, Santos MA, Lima TC, et al. Disparities in Acute Myocardial Infarction Treatment Between Users of the Public and Private Healthcare System in Sergipe. Int J Cardiovasc Sci. 2018;31(4)339-358.
15. Oliveira JC, Santos MA, Oliveira J, Oliveira LC, Barreto ID, Lima TC, et al.Disparities in Access and Mortality of Patients With ST - Segment–Elevation Myocardial Infarction Using the Brazilian Public Healthcare System: VICTIM Register. J Am Heart Assoc. 2019;8(20).
16. Nicolau JC, Franken M, Lotufo PA, Carvalho AC, Neto JAM, Lima FG, et al. Utilização de Terapêuticas Comprovadamente Úteis no Tratamento da Coronariopatia Aguda: Comparação entre Diferentes Regiões Brasileiras. Análise do Registro Brasileiro de Síndromes Coronarianas Agudas (BRACE – Brazilian Registry on Acute Coronary Syndromes). Arq Bras Cardiol. 2012;98(4):282-289.
17. Welsh RC, Van de Werf F, Westerhout CM, Goldstein P, Gershlick AH, Wilcox RG, et al. Outcomes of a Pharmacoinvasive Strategy for Successful Versus Failed Fibrinolysis and Primary Percutaneous Intervention in Acute Myocardial Infarction (from the Strategic Reperfusion Early After Myocardial Infarction [STREAM] Study). Am J Cardiol. 2014;114(6):811-819.
18. D'onofrio G, Safdar B, Lichtman JH, Strait KM, Dreyer RP, Geda M, et al. Sex Differences in Reperfusion in Young Patients With ST-Segment-Elevation Myocardial Infarction. Circulation. 2015; 131(15):1324-1332.

19. Parker AB, Naylor CD, Chong A, Alter DA. Socio-Economic Status and Acute Myocardial Infarction Study Group Clinical prognosis, pre-existing conditions and the use of reperfusion therapy for patients with ST segment elevation acute myocardial infarction. Can J Cardiol.2006;22(2):131-9.

20. Dey S, Flather MD, Devlin G, Brieger D, Gurfinkel EP, Steg PG, et al. Global Registry of Acute Coronary Events investigators. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the Global Registry of Acute Coronary Events. Heart. 2009; 95(1):20-6.

21. Damasceno CA, Mussi FC. Fatores de retardo pré-hospitalar no infarto do miocárdio: uma revisão de literatura. Cienc Cuid Saude. 2010; 9(4):821.

22. Calé R, de Sousa L, Pereira H, CostaM, Almeida MS. Angioplastia primária na mulher: realidade nacional. Rev Port Cardiol. 2014;33(6):353-61.

23. Nguyen HL, Saczynski JS, Gore JM, Goldberg RJ. Age and sex differences in duration of prehospital delay in patients with acute myocardial infarction a systematic review. Circ Cardiovasc Qual Outcomes. 2010;3(1):82–92.

24. Weaver WD, White HD, Wilcox RG, Aylward PE, Morris D, Guerci A, et al. Comparisons of characteristics and outcomes among women and men with acute myocardial infarction treated with thrombolytic therapy: GUSTO-I investigators. *JAMA*. 1996;275(10):777–82.

25. Huded CP, Johnson M, Kravitz K, Menon V, Abdallah M, Gullet TC, et al. 4-Step Protocol for Disparities in STEMI Care and Outcomes in Women**.** J Am Coll Cardiol. 2018; 71(19):2122-32.

26. Barbosa RR, Silva VR, Renato RG, Cesara FB, Mauroa VF, Bayerla DMR, et al. Diferenças de gênero nos resultados da intervenção coronariana percutânea primaria em pacientes com infarto do miocárdio com elevação de ST. Rev Bras Cardiol Invasiva. 2015;23(2):96-101.

Gender Equity in Access to Reperfusion in Acute Myocardial Infarction: Still A Long Way to Go

Clara L. Fraga,[1] Frederico V. B. Macedo,[1] Rodrigo T. L. Rocha,[1] Domingos Sávio G. Ferreira Filho,[1] Bruno R. Nascimento[1,2]

Faculdade de Medicina, Universidade Federal de Minas Gerais,[1] Belo Horizonte, MG - Brazil

Hospital das Clínicas, Universidade Federal de Minas Gerais,[2] Belo Horizonte, MG - Brazil

Short Editorial related to the article: Access to Reperfusion Therapy and Mortality in Women with ST-Segment–Elevation Myocardial Infarction: VICTIM Register

Ischemic heart disease is the main cause of death worldwide, and its most severe presentation ST-elevation acute myocardial infarction (STEMI), which corresponds to approximately 1/3 of the presentations,[1] and early reperfusion is the main strategy for reducing mortality. Despite broad historical knowledge of gender-related differences in treatment and prognosis of patients with an acute presentation of ischemic heart disease, male individuals, in addition to having earlier access to health systems, are even more likely to undergo a diagnostic coronary angiography and urgent revascularization than women.[2-4] The article "Access to Reperfusion Therapies and Mortality in Women with Acute Myocardial Infarction with ST-Segment Elevation: the VICTIM Registry[5]" demonstrates very well this difference in access to reperfusion therapies in the Brazilian scenario. When evaluating 878 patients admitted with STEMI in the northeastern state of Sergipe, Brazil, it was observed that female individuals were less frequently submitted to reperfusion strategies when compared to males, both primary percutaneous coronary interventions (PCI) (44% x 54.5%; p = 0.003) and fibrinolysis (1.7% x 2.6%; p = 0.422). This scenario is in line with data from other previous studies on this topic carried out in different settings (Table 1). In the VICTIM[5] registry, higher in-hospital mortality was observed in the female gender (16.1% x 6.7*; p <0.001), probably as a consequence of this lower access to reperfusion therapies. These data are consistent with systematic reviews of the literature on the topic.[6]

Would the delay in calling for help be one of the reasons why women are less frequently submitted to revascularization therapies? The aforementioned study demonstrated that this does not seem to have been the problem in Sergipe, with the time spent calling for help after symptom onset being statistically similar between the genders. However, female patients underwent a greater delay in the primary hospital, until referral to a unit with infrastructure to perform the percutaneous reperfusion (transfer delay). These data differ in part from the findings of a recent study carried out in Italy, in which the mean time from symptom onset to presentation at the hospital was longer for women (280 x 240 minutes), with only 23.2% of women x 29.1 % of men undergoing a delay <120 minutes until hospital admission (p = 0.002).[7] As in the VICTIM study, there was an impact on mortality: in cases with delay ≥120 minutes, mortality rates were higher among women (5.5% x 2.8%), whereas in cases with presentation <120 minutes, mortality was considerably lower and statistically similar between genders (2.0% in women vs. 1.6% in men).[7]

Moreover, the present study observed that STEMI tends to affect women who are older (> 63 years) and with a greater number of risk factors, when compared to men.[5] As demonstrated in a previous publication with data from Brazil, women also have a higher level of stress, which may increase the risk for acute events.[8] A similar pattern was observed in studies carried out in Australia and Italy, which showed that women are more likely to have STEMI at an older age and to have higher rates of hypertension, diabetes and/or hypercholesterolemia, in contrast to lower rates of smoking.[7,9] In these publications, it is questioned whether the underestimation of female cardiovascular risk may have resulted in more conservative treatments, contributing to unfavorable outcomes.[7,9] Similarly, other authors question whether the patients' advanced age, associated with a greater number of comorbidities, together with less typical clinical presentations, would influence the choice of conservative treatment in women.[10,11]

In this context, the data from the VICTIM study also draw attention to the importance of a lower threshold of suspicion for ordering tests and indicating invasive procedures for female patients.[5] As demonstrated in a Swiss study with 51,725 patients, over a period of 19 years (1997 - 2016), in-hospital mortality significantly decreased from 9.8% to 5.5% in men and from 18.3% to 6.9% in women, as a result of the increasing indication for reperfusion therapies (thrombolysis or PCI) in STEMI: from 60% to 93% (p <0.001) in men and from 45% to 90% (p <0.001) in women[12,13] – with a proportionally greater increase among men. These data reinforce the importance of a detailed and individualized clinical judgment in the emergency setting.

That said, the study implications for the medical community and attending physicians are straightforward: the multiple comorbidities, older age and atypical presentations should not be a barrier to the indication of reperfusion therapies, and the

Keywords

Myocardial Ischemia; Myocardial Infarction; Myocardial Revascularization; Myocardial Reperfusion; Womens; Men.

Mailing Address: Bruno R. Nascimento •
Hospital das Clínicas da Universidade Federal de Minas Gerais - Serviço de Cardiologia e Cirurgia Carvdiovascular e Centro de Telessaúde - Avenida Professor Alfredo Balena, 110, 1º andar. Postal Code 30130-100, Belo Horizonte. MG – Brazil
E-mail: ramosnas@gmail.com

DOI: https://doi.org/10.36660/abc.20210082

Table 1 – Access to reperfusion therapies in acute myocardial infarction with ST-segment elevation, by gender

Study	VICTIM Registry[5]	Radovanovic et al.[11]	Hansen et al.[12]	Soeiro et al.[1]
PCI (%, men x women)	54.5 x 44	36.6 x 27.2	58 x 72	44.9 x 35.4
Fibrinolysis (%, men x women)	2.6 x 1.7	18.7 x 15.2	N/A	N/A
Mortality (%, men x women)	16.1 x 6.7	10.7 x 6.3	11 x 7	3.7 x 3.1

PCI: percutaneous coronary intervention.

clinical condition should be analyzed as a whole. Additionally, public policies should be proposed to allow for a faster referral of these patients to a service with intervention a facilities, in addition to health education programs and awareness of cardiovascular symptoms, focused on women. With these multifaceted actions, greater access to reperfusion may result in further reductions in mortality from cardiovascular diseases, especially among women, in the coming years.

References

1. Soeiro am, silva p, roque eac, bossa as, biselli b, leal t et al. Prognostic differences between men and women with acute coronary syndrome. Data from a brazilian registry. Arq bras cardiol. 2018; 111(5): 648-53.
2. Radovanovic d, erne p, urban p, bertel o, rickli h, gaspoz jm et al. Gender differences in management and outcomes in patients with acute coronary syndromes: results on 20.290 patients from the amis plus registry. Heart. 2007; 93(11): 1.369-75.
3. Soares gp. Analysis of a population-based registry of hospitalizations for acute myocardial infarction. Arq bras cardiol. 2020; 115(5): 925-6.
4. Alves l, polanczyk ca. Hospitalization for acute myocardial infarction: a population-based registry. Arq bras cardiol. 2020; 115(5): 916-24.
5. Oliveira JC, Barros MPS, Barreto IDC, Silva Filho RC, Andrade VA, Oliveira AM et al. Acesso à Terapia de Reperfusão e Mortalidade em Mulheres com Infarto Agudo do Miocárdio com Supradesnivelamento do Segmento ST: Registro VICTIM. Arq Bras Cardiol. 2021; 116(4):695-703.
6. Van der meer mg, nathoe hm, van der graaf y, doevendans pa, appelman y. Worse outcome in women with stemi: a systematic review of prognostic studies. Eur j clin invest. 2015; 45(2): 226-35.
7. Cenko e, van der schaar m, yoon j, kedev s, valvukis m, vasiljevic z et al. Sex-specific treatment effects after primary percutaneous intervention: a study on coronary blood flow and delay to hospital presentation. J am heart assoc. 2019; 8(4): e011190.
8. Schmidt k, lima ads, schmitt kr, moraes ma, schmidt mm. Stress in women with acute myocardial infarction: a closer look. Arq bras cardiol. 2020; 115(4): 649-57.
9. Worrall-carter l, mcevedy s, wilson a, rahman ma. Gender differences in presentation, coronary intervention, and outcomes of 28.985 acute coronary syndrome patients in victoria, australia. Womens health issues. 2016; 26(1): 14-20.
10. Dey s, flather md, devlin g, brieger d, gurfinkel ep, steg pg et al. Sex-related differences in the presentation, treatment and outcomes among patients with acute coronary syndromes: the global registry of acute coronary events. Heart. 2009; 95(1): 20-6.
11. Shaw lj, miller dd, romeis jc, kargl d, younis lt, chaitman br. Gender differences in the noninvasive evaluation and management of patients with suspected coronary artery disease. Ann intern med. 1994; 120(7): 559-66.
12. Radovanovic d, seifert b, roffi m, urban p, rickli h, pedrazzini g et al. Gender differences in the decrease of in-hospital mortality in patients with acute myocardial infarction during the last 20 years in switzerland. Open heart. 2017; 4(2): e000689.
13. Hansen kw, soerensen r, madsen m, madsen jk, jensen js, von kappelgaard lm et al. Developments in the invasive diagnostic-therapeutic cascade of women and men with acute coronary syndromes from 2005 to 2011: a nationwide cohort study. Bmj open. 2015; 5(6): e007785.

Cardiovascular Risk Misperception and Low Awareness of Familial Hypercholesterolemia in Individuals with Severe Hypercholesterolemia

Raul D. Santos,[1,2] Carolina Pereira,[3] Fernando Cesena,[1] Antonio Gabriele Laurinavicius,[1] Viviane Tabone,[1] Marcio Sommer Bittencourt[1]

Hospital Israelita Albert Einstein,[1] São Paulo, SP - Brazil

Instituto do Coração (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de Sao Paulo,[2] São Paulo, SP - Brazil

Escola de Enfermagem Anna Nery, Universidade Federal do Rio de Janeiro,[3] Rio de Janeiro, RJ - Brazil

Abstract

Background: **Individuals with severe hypercholesterolemia are at a high risk of developing atherosclerotic cardiovascular disease (ASCVD). Many of them have familial hypercholesterolemia (FH).**

Objectives: **To assess from a patient perspective the degree of awareness about severe hypercholesterolemia, especially FH, ASCVD risk perception, cascade screening performance, and treatment of individuals participating in a routine health evaluation program.**

Methods: **From a database of 70,000 Brazilian individuals evaluated between 2006 and 2016, 1,987 (2.8%) met the inclusion criteria (age ≥ 18 years and LDL-C ≥ 190 mg/dL or ≥ 160 mg/dL, respectively, if not in use of statins or on statin therapy). Two-hundred individuals were randomly invited to complete an extensive questionnaire. FH was diagnosed if suspected by the attending physician.**

Results: **Although 97% of the sample (age 48±9 years; 16% women; 95% college/university education; 88% primary prevention; LDL-C 209±47 mg/dL) had severe hypercholesterolemia, only 18% and 29.5% believed to be at high ASCVD risk and reported knowledge of their recommended LDL-C goal, respectively. Fifty-eight percent reported being informed that high cholesterol could be a family disease, 24.5% (n = 49) had ever heard about FH, and merely 14% (n = 29) had been previously identified as suspected of having FH (age at FH diagnosis 35±12 years; 79% and 31% diagnosed, respectively, > 30 and > 40 years old). Only 2.5% underwent genetic tests, 17% underwent cascade screening, and 17% were not in use of pharmacological treatment.**

Conclusions: **An important gap in risk perception, cholesterol management, and aspects related to FH was encountered in individuals with severe hypercholesterolemia. (Arq Bras Cardiol. 2021; 116(4):706-712)**

Keywords: **Hypercholesterolemia Risk Factors; Hyperlipoproteinemia Type II; Atherosclerosis; Mass Screening.**

Introduction

Hypercholesterolemia is a proven causal factor of atherosclerotic cardiovascular disease (ASCVD).[1] Both Brazilian and US guidelines[2,3] classify individuals with severe hypercholesterolemia (low-density lipoprotein cholesterol - LDL-C > 190 mg/dL) as being at a high risk of developing ASCVD, especially coronary heart disease. Among these, many individuals may suffer from heterozygous familial hypercholesterolemia (FH), an autosomal dominant disease affecting approximately 1/250 individuals in general.[4,5] FH is characterized by elevated LDL-C concentrations since birth and is associated with a 10-13-fold higher risk of ASCVD onset in the general population.[4,6] It is widely accepted that FH is currently mishandled in most countries.[7,8] However, epidemiologic data are still scarce,[9,10] and estimations on prevalence, diagnosis, treatment, and control in different parts of the world continue to rely predominantly on experts' opinion.

Routine health evaluation programs provide a good opportunity to diagnose hypercholesterolemia and, consequently, FH. The identification of an index case can start cascade screening with the aim of identifying affected members within a given FH family.[11] However, most hypercholesterolemic individuals are unaware of FH, family dominance and distribution, and consequent yet preventable high ASCVD risk.[12]

The aim of the present study was to assess the degree of awareness of ASCVD risk in patients with severe hypercholesterolemia, especially in those suspected of having

Mailing Address: Raul D. Santos •
Hospital Israelita Albert Einstein - Av. Albert Einstein, 627. Postal Code 05652-900, São Paulo, SP - Brazil
E-mail: rauldsf@gmail.com
Manuscript received August 07, 2019, revised manuscript January 23, 2020, accepted February 03, 2020

DOI: https://doi.org/10.36660/abc.20190516

FH participating in a routine health evaluation program. On the latter we also evaluated if measures of care in FH such as cascade screening and use of pharmacological treatment were adequately performed according to disease management guidelines.[2]

Methods

From a database of 70,000 Brazilian individuals undergoing a mandatory employer-sponsored routine health evaluation between 2006 and 2016 at the Hospital Israelita Albert Einstein in São Paulo, Brazil, 1,987 (2.8%) met the inclusion criteria (age ≥ 18 years and fasting LDL-C ≥ 190 mg/dL without statins or ≥ 160 mg/dL if on statin therapy). Of these, 200 individuals were randomly invited by phone or e-mail to participate in the study during 2017. The random procedure consisted of generating a random sequence number, ordering participants by those numbers, and then calling them following the random order. The study sample was selected by convenience; if subjects accepted to participate, an oral informed consent was obtained and an interview was performed by telephone according to a structured questionnaire developed for the present study (Supplemental Material). If the individual refused to participate or could not be contacted, the next on the randomization list was invited to participate. This study was approved by the Ethics Committee of Hospital Israelita Albert Einstein.

The health evaluation protocol was previously described and consisted of clinical and laboratory evaluations.[13] The structured survey (Supplementary Material) included questions about hypercholesterolemia, FH awareness, diagnosis, adherence to treatment, cascade screening in first-degree relatives, and ASCVD risk perception from a patient perspective. FH was considered suspected if the attending physician suggested or made this diagnosis.

Statistical Analysis

This is a descriptive study, and data normality was assessed using the Kolmogorov-Smirnov test with a significance level of 5%. Continuous variables are presented as mean and standard deviation or as median and quartiles for variables known not to be normally distributed. Categorical variables are presented as absolute counts and proportions. Age at diagnosis is presented in a histogram. Statistical analysis was performed using Stata version 14.0 (StataCorp, USA).

Results

General characteristics of participants with severe hypercholesterolemia

Table 1 shows clinical and laboratory characteristics of the 200 enrolled participants and the 29 (14.5%) individuals in which FH was suspected. Figure 1 (Central Illustration) summarizes the study results. Overall, most individuals were men, 95% had college/university degree, and 12% (n= 24) had suffered a previous ASCVD event (myocardial infarction, angina, myocardial revascularization, or stroke). Ninety-seven percent (n = 195) were aware of having very high cholesterol levels and 58% (n = 116) had been informed by their physicians that high cholesterol could be a family disease. Indeed, 76% (n = 152) reported having a first-degree relative with high cholesterol. However, only 4.5% (n = 9) had their

Table 1 – Clinical and laboratory characteristics of hypercholesterolemic individuals and of those suspected of FH

	General (n = 200)	Suspected FH (n = 29)
Age (years)	48±9	44±9
Female sex n (%)	34 (16%)	6 (23%)
Hypertension n (%)	21 (11%)	1 (4%)
Diabetes n (%)	7 (3.5%)	0
Smokers n (%)	26 (13%)	5 (19%)
Previous ASCVD n (%)	24 (12%)	4 (14%)
Current lipid-lowering therapy n (%)	125 (62.5%)	24 (83%)
Age lipid-lowering therapy was started (years)	41.2 ± 9.6	36.6±11.1
First-degree relatives screened for high cholesterol	9 (4.5%)	5 (17%)
Total cholesterol (mg/dL)	290±32	307±58
HDL-C (mg/dL)	47±13	48±13
LDL-C (mg/dL)	209±47	224±55
Triglycerides (mg/dL)	139 (106 – 212)	142 (97 – 232)
Glucose (mg/dL)	95±30	87±7
HbA1c %	5.7±0.9	5.5±0.3

Descriptive statistics only; no formal comparison was made between the groups because of patient duplicity. Continuous data expressed as mean ± standard deviation, except for triglycerides, expressed as median and quartiles; categorical data expressed as frequencies (%). ASCVD: atherosclerotic cardiovascular disease; FH: familial hypercholesterolemia; HbA1c: glycated hemoglobin; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

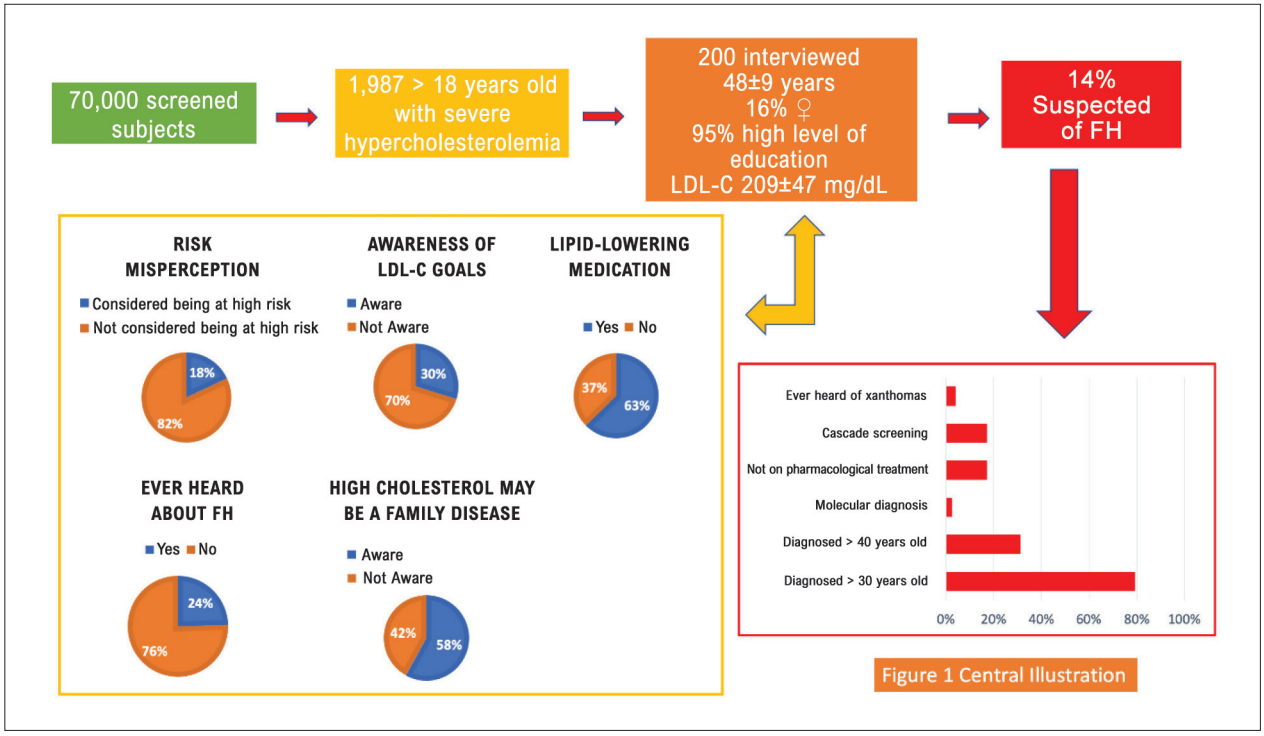


Figure 1 – *Central Illustration summarizes main study results in the entire study population (n = 200) and in those suspected of FH (n = 29). FH: familial hypercholesterolemia; LDL-C: low-density lipoprotein cholesterol.*

first-degree relatives invited to test their blood cholesterol levels and confirm that information.

Although 42.5% (n = 85) reported having a first-degree relative with a previous manifestation of ASCVD, only 19 (9.5%) recalled such event occurring before the age of 55 years. Overall, despite very high cholesterol levels, only 18% (n = 36) considered themselves as being at high ASCVD risk, while 43.5% (n = 87) believed to be at low risk for the next 10 years. When asked about the health implications of having high cholesterol, only 11% (n = 22) considered high cholesterol more important than diabetes or hypertension as risk factors for ASCVD, while 71% (n = 139) considered diabetes as the most severe of the three conditions.

Most interviewed individuals attended regular medical consultations; 72.5% (n = 145) consulted their physicians and 73% (n = 146) had their cholesterol levels determined in the past year. However, only 34.5% (n = 69) reported knowing their last cholesterol test results. Only 29.5% (n = 59) reported knowledge about their recommended LDL-C goal according to individual ASCVD risk status. Interestingly, of those, only 1 (1.7%), 9 (15%), 4 (6.8%), and 3 (5.1%) individuals identified LDL-C values < 70 mg/dL, < 100 mg/dL, < 130 mg/dL, and < 160 mg/ dL as possible recommended goals according to risk, respectively.[2,14]

Thirty-nine percent (n = 78) underwent a dietary change before pharmacological lipid-lowering therapy was initiated, and the therapy was being used by 62.6% (n = 125). Of those using lipid-lowering medications, 78% (n = 100) reported taking their medications on a daily basis. Eighty-five percent (n = 110) had changed medication doses to further increase cholesterol lowering, while 15% (n = 19) reported adverse events. Reported reasons for stopping medications were patients' own decision (54.8%), adverse events (22.6%), medical orientation (19.4%), and others (3.2%).

Individuals with suspected FH

Only 24.5% (n = 49) of hypercholesterolemic subjects had ever heard about FH and, of those, 29 (59%) had been previously identified as suspected of having FH by their healthcare providers. Mean age (SD) when suspected FH was diagnosed was 35±12 years. Figure 2 shows the distribution of age when FH was diagnosed; 79% and 31% were diagnosed, respectively, after the age of 30 and 40 years. Genetic diagnosis was performed only in 5 (17.2%) of those suspected of having FH, and only 2 individuals (4%) had ever heard about xanthomas. Importantly, although 27 (93%) individuals with suspected FH reported having been told that other family members could have this disease, only 5 (17%) recalled having their relatives invited to test their blood cholesterol. Treatment was started on average after the age of 35 years (Table 1), and 17% (n = 5) of those suspected of having FH were not in use of pharmacological lipid-lowering therapy.

Discussion

There are no data for the Brazilian population on patient awareness of implications of hypercholesterolemia, especially severe forms such as FH. Most studies thus far evaluated overall awareness of hypercholesterolemia diagnosis and not specific

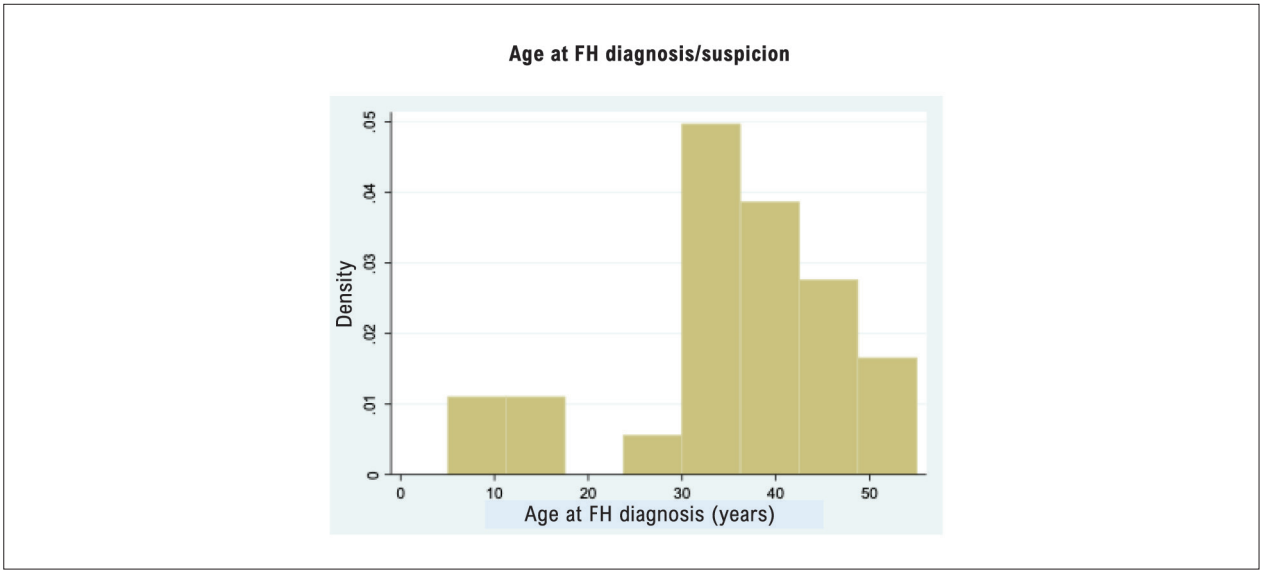


Figure 2 – *Frequency of age when FH was suspected/diagnosed. FH: familial hypercholesterolemia.*

knowledge of the severe forms and their consequences.[15,16] This survey, performed in a highly educated, predominantly male population with severe hypercholesterolemia attending a health evaluation program in São Paulo, suggests that awareness of implications of very high blood cholesterol and, especially, FH and its related aspects is low.

Most striking were the findings of patient misperception or lack of knowledge about the high risk associated with severe hypercholesterolemia, as only one in five individuals recognized being at high ASCVD risk, despite medical guideline recommendations stating otherwise.[2,3,14] In addition, there was a lack of knowledge regarding recommended LDL-C goals for their level of risk and no use of pharmacological treatment in almost 40% of the study participants. Another concerning finding was that, among those who stopped their medications, almost 75% did so by their personal decision or medical orientation rather than occurrence of adverse events. One possible explanation for these findings is that only one in 10 of the study participants considered high cholesterol as the most important risk factor in comparison with diabetes and hypertension. Despite the role played by the latter, there is no doubt about the central and causal role of hypercholesterolemia and consequent elevated risk attributed to the severe forms, especially FH, in coronary heart disease.[1,17,18] These findings suggest the need for improvement in literacy about the role played by cholesterol in ASCVD. As previously shown, lack of literacy about chronic diseases such as hypercholesterolemia is associated with inadequate use of pharmacological treatment in low-income countries, where medication costs have important implications.[19,20] This is even more concerning considering the elevated social and educational level of the study participants.

FH is severely underdiagnosed and undertreated,[4,7] and late diagnosis (usually > 40 years old)[21] and consequent late treatment are associated with elevated rates of coronary heart disease, as seen in index cases in Brazil[22] and other countries.[10] Indeed, there is evidence that even in individuals with severe hypercholesterolemia, i.e., LDL-C > 190 mg/dL, the presence of an autosomal dominant genetic defect implicates in a 4-fold greater relative risk of ASCVD.[17] Considering the autosomal dominant trait of FH, an adequate model of care for this disease includes not only identification and treatment of index cases but cascade screening for affected relatives.[7]

This study suggests that there is a low level of FH awareness amongst individuals with severe hypercholesterolemia, as only 1 in 4 study participants reported knowledge about the disease. This occurs despite a high reported prevalence of elevated cholesterol in first-degree relatives. Moreover, in those with suspected FH, the disease was diagnosed late, which probably explains the elevated frequency of ASCVD in the population.

There was a very low indication for cascade screening by attending physicians, and almost 20% of patients with suspected FH were not in use of pharmacological therapy. These findings do not differ much from those of a recent study of individuals undergoing molecular cascade screening due to FH suspicion in a tertiary center in Brazil.[23] In the study conducted by Souto et al., only 20% of either index cases or first-degree relatives participating in the cascade screening program reported a previous suspicion of FH diagnosis, while 71% where in use of pharmacological lipid-lowering treatment.

In the US Cascade Screening for Awareness and Detection (CASCADE) of FH registry,[24] there was a median 6-year gap between diagnosis of hypercholesterolemia and start of lipid-lowering treatment and subsequent FH diagnosis. These results are compatible with the findings of the current study, in which severe hypercholesterolemia was diagnosed; pharmacological treatment was suggested/started in most study participants, but only one quarter had ever heard about FH from their physicians. Our results suggest an important gap in FH literacy not only among patients but

also among physicians. Indeed, a poor knowledge about FH amongst either physicians[25-27] or patients[28] has been reported in different parts of the world, including Brazil.

Limitations of this study include the relatively small sample, but it is worth noting that LDL-C > 190 mg/dL usually affects around 5% of the population; the cross-sectional design shows only associations and there was no formal investigation of the causes of our findings; the specific characteristics of the population, especially high educational level, does not allow that results to be extrapolated for the overall Brazilian population with lower educational level, but it may suggest that more severe findings may be encountered; a direct comparison of risk perception and management between those suspected or not of FH was not performed; finally, although study participants were actively questioned, results are subject to recall bias. Nonetheless, findings are remarkable and compatible with other investigations[24-28] and show an important unmet need for education about the importance of severe hypercholesterolemia and, specifically, FH.

Conclusions

An important gap in risk perception, cholesterol management, and aspects related to FH was encountered in individuals with severe hypercholesterolemia. Further and broader investigations are necessary to confirm the results, and development of education programs for both patients and physicians will be required to close this knowledge gap.

Author contributions

Conception and design of the research: Santos RD, Laurinavicius AG, Tabone V, Bittencourt MS; Data acquisition: Pereira C, Cesena F; Analysis and interpretation of the data: Santos RD, Pereira C, Cesena F, Bittencourt MS; Obtaining financing: Laurinavicius AG; Writing of the manuscript: Santos RD, Bittencourt MS; Critical revision of the manuscript for intellectual content: Santos RD, Pereira C, Cesena F, Laurinavicius AG, Tabone V.

Potential Conflict of Interest

Raul D. Santos has received honoraria related to consulting, research and or speaker activities from: Amgen, Astra Zeneca, Esperion, Kowa, Merck, MSD, Novo-Nordisk, Abbott, Pfizer, EMS, GETZ Pharma, LIbbs, Novartis and Sanofi Regeneron.

Antonio Gabriele Laurinavicius is a former employee of Sanofi.

Marcio Sommer Bittencourt has received honoraria from Boston Scientific.

Sources of Funding

This study was funded by Sanofi.

Study Association

This study is not associated with any thesis or dissertation.

References

1. Ference BA, Ginsberg HN, Graham I, Ray KK, Packard CJ, Bruckert E, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease. 1. Evidence from genetic, epidemiologic, and clinical studies. A consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J. 2017;38(32):2459-72.
2. Faludi AA, Izar MCO, Saraiva JFK, Chacra APM, Bianco HT, Afiune AN, et al. Atualização da Diretriz Brasileira de Dislipidemias e Prevenção da Aterosclerose – 2017. Arq Bras Cardiol. 2017;109(2 Supl 1):1-76.
3. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2889-934.
4. Defesche JC, Gidding SS, Harada-Shiba M, Hegele RA, Santos RD, Wierzbicki AS. Familial hypercholesterolaemia. Nat Rev Dis Primers. 2017;3:17093.
5. Harada PH, Miname MH, Bensenor IM, Santos RD, Lotufo PA. Familial hypercholesterolemia prevalence in an admixed racial society: Sex and race matter. The ELSA-Brasil. Atherosclerosis. 2018;277:273-7.
6. Benn M, Watts GF, Tybjaerg-Hansen A, Nordestgaard BG. Familial hypercholesterolemia in the danish general population: prevalence, coronary artery disease, and cholesterol-lowering medication. J Clin Endocrinol Metab. 2012;97(11):3956-64.
7. Nordestgaard BG, Chapman MJ, Humphries SE, Ginsberg HN, Masana L, Descamps OS, et al. Familial hypercholesterolaemia is underdiagnosed and undertreated in the general population: guidance for clinicians to prevent coronary heart disease: consensus statement of the European Atherosclerosis Society. Eur Heart J. 2013;34(45):3478-90a.
8. Vallejo-Vaz AJ, Kondapally Seshasai SR, Cole D, Hovingh GK, Kastelein JJ, Mata P, et al. Familial hypercholesterolaemia: A global call to arms. Atherosclerosis. 2015;243(1):257-9.
9. Collaboration EASFHS, Investigators EASFHSC. Overview of the current status of familial hypercholesterolaemia care in over 60 countries - The EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). Atherosclerosis. 2018;277:234-55.
10. Pang J, Chan DC, Hu M, Muir LA, Kwok S, Charng MJ, et al. Comparative aspects of the care of familial hypercholesterolemia in the "Ten Countries Study". J Clin Lipidol. 2019;13(2):287-300.
11. Santos RD, Frauches TS, Chacra AP. Cascade Screening in Familial Hypercholesterolemia: Advancing Forward. J Atheroscler Thromb. 2015;22(9):869-80.
12. Besseling J, Hovingh GK, Huijgen R, Kastelein JJ, Hutten BA. Statins in Familial Hypercholesterolemia: Consequences for Coronary Artery Disease and All-Cause Mortality. J Am Coll Cardiol. 2016;68(3):252-60.
13. Fernandes RA, Ritti-Dias RM, Balagopal PB, Conceicao RDO, Santos RD, Cucato GG, et al. Self-initiated physical activity is associated with high sensitivity C-reactive protein: A longitudinal study in 5,030 adults. Atherosclerosis. 2018;273:131-5.
14. Sociedade Brasileira de Cardiologia, Xavier HT, Izar MC, Faria Neto JR, Assad MH, Rocha VZ, et al. [V Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis]. Arq Bras Cardiol. 2013;101(4 Suppl 1):1-20.
15. Lotufo PA, Santos RD, Sposito AC, Bertolami M, Rocha-Faria JN, Izar MC, et al. Self-Reported High-Cholesterol Prevalence in the Brazilian Population: Analysis of the 2013 National Health Survey. Arq Bras Cardiol. 2017;108(5):411-6.

16. Fontanelli MM, Nogueira LR, Garcez MR, Sales CH, Corrente JE, Cesar CLG, et al. [Validity of self-reported high cholesterol in the city of Sao Paulo, Brazil, and factors associated with this information's sensitivity]. Cad Saude Publica. 2018;34(12):e00034718.

17. Khera AV, Won HH, Peloso GM, Lawson KS, Bartz TM, Deng X, et al. Diagnostic Yield and Clinical Utility of Sequencing Familial Hypercholesterolemia Genes in Patients With Severe Hypercholesterolemia. J Am Coll Cardiol. 2016;67(22):2578-89.

18. McGorrian C, Yusuf S, Islam S, Jung H, Rangarajan S, Avezum A, et al. Estimating modifiable coronary heart disease risk in multiple regions of the world: the INTERHEART Modifiable Risk Score. Eur Heart J. 2011;32(5):581-9.

19. Bowry AD, Shrank WH, Lee JL, Stedman M, Choudhry NK. A systematic review of adherence to cardiovascular medications in resource-limited settings. J Gen Intern Med. 2011;26(12):1479-91.

20. Murphy A, Faria-Neto JR, Al-Rasadi K, Blom D, Catapano A, Cuevas A, et al. World Heart Federation Cholesterol Roadmap. Glob Heart. 2017;12(3):179-97 e5.

21. Santos RD, Gidding SS, Hegele RA, Cuchel MA, Barter PJ, Watts GF, et al. Defining severe familial hypercholesterolaemia and the implications for clinical management: a consensus statement from the International Atherosclerosis Society Severe Familial Hypercholesterolemia Panel. Lancet Diabetes Endocrinol. 2016;4(10):850-61.

22. Jannes CE, Santos RD, de Souza Silva PR, Turolla L, Gagliardi AC, Marsiglia JD, et al. Familial hypercholesterolemia in Brazil: cascade screening program, clinical and genetic aspects. Atherosclerosis. 2015;238(1):101-7.

23. Souto AC, Miname MH, Fukushima J, Jannes CE, Krieger JE, Hagger M, et al. Health related quality of life in individuals at high risk for familial hypercholesterolemia undergoing genetic cascade screening in Brazil. Atherosclerosis. 2018;277:464-9.

24. deGoma EM, Ahmad ZS, O'Brien EC, Kindt I, Shrader P, Newman CB, et al. Treatment Gaps in Adults With Heterozygous Familial Hypercholesterolemia in the United States: Data From the CASCADE-FH Registry. Circ Cardiovas Gen. 2016;9(3):240-9.

25. Batais MA, Almigbal TH, Bin Abdulhak AA, Altaradi HB, AlHabib KF. Assessment of physicians' awareness and knowledge of familial hypercholesterolemia in Saudi Arabia: Is there a gap? PLoS One. 2017;12(8):e0183494.

26. Pang J, Hu M, Lin J, Miida T, Nawawi HM, Park JE, et al. An enquiry based on a standardised questionnaire into knowledge, awareness and preferences concerning the care of familial hypercholesterolaemia among primary care physicians in the Asia-Pacific region: the "Ten Countries Study". BMJ Open. 2017;7(10):e017817.

27. Zimmerman J, Duprez D, Veach PM, Zierhut HA. Barriers to the identification of familial hypercholesterolemia among primary care providers. J Community Genet. 2019;10(2):229-36.

28. Hagger MS, Hardcastle SJ, Hu M, Kwok S, Lin J, Nawawi HM, et al. Health literacy in familial hypercholesterolemia: A cross-national study. Eur J Prev Cardiol. 2018;25(9):936-43.

*Supplemental Materials

For additional information, please click here.

The Unknown Risk of Familial Hypercholesterolemia in the Development of Atherosclerotic Cardiovascular Disease

Elizabeth do Nascimento[1] *and José Luiz de Brito Alves*[2]

Departamento de Nutrição, Centro de Ciências da Saúde, Universidade Federal de Pernambuco,[1] *Recife, PE - Brazil*
Departamento de Nutrição, Centro de Ciências da Saúde, Universidade Federal da Paraíba,[2] *João Pessoa, PB - Brazil*

Short Editorial related to the article: Cardiovascular Risk Misperception and Low Awareness of Familial Hypercholesterolemia in Individuals with Severe Hypercholesterolemia

Cardiovascular diseases (CVD) are recognized as the main causes of death in adulthood in the world.[1,2] A number of factors, such as smoking, arterial hypertension, obesity, metabolic syndrome and hypercholesterolemia have been described as important risk factors in the development of CVD and premature death.[3] Hypercholesterolemia can be classified as primary or secondary in origin. Primary hypercholesterolemia is due to genetically determined defects in lipid or lipoprotein metabolism; secondary hypercholesterolemia can be caused by inadequate lifestyle, diseases or medications.[3]

Familial hypercholesterolemia (FH) is an autosomal-dominant disorder characterized by mutations in genes in the encoding of proteins involved in low-density lipoprotein (LDL) metabolism that occur in the presence of high plasma cholesterol and LDL levels associated with clinical signs of tendon xanthoma. FH is responsible for approximately 10% of cardiovascular events in people under 50 years of age.[4-6] In FH, mutations may be present in the LDL receptor gene, in the gene-encoding Apoprotein B-100 or in autosomal recessive LDLRAP1 gene and in autosomal dominant familial hypercholesterolemia (HCHOLA3) variant of the PCSK9 gene.[7] These mutations lead to an impairment in the apoprotein-receptor interaction and result in high plasma cholesterol, high LDL levels and risk of development of atherosclerotic disease.[5,8]

FH is one of the most common monogenic diseases, recognized by the World Health Organization as a worldwide public health problem. Despite its widespread incidence, early diagnosis of FH is still not widely performed and, consequently, the adoption of preventive treatments for hypercholesterolemia is impaired.[9] Therefore, it is reasonable to suggest that early diagnosis of FH and appropriate treatment are essential to prevent or at least delay the onset of cardiovascular events. Cascade screening of FH is a crucial and cost-effective way to prevent atherosclerotic processes and should be performed in all of the first, second and third-degree relatives of patients diagnosed with FH.

The importance of screening and early treatment of FH has been a target of concern in the scientific community. In a recent manuscript, Santos Filho et al.[10] investigated whether Brazilian subjects with hypercholesterolemia knew the risk of developing CVD and whether they had family history.[10]

To answer this question, the authors used a database of 70.000 Brazilian individuals who had undergone a mandatory routine health assessment between 2006 and 2016 at Hospital Israelita Albert Einstein in São Paulo, Brazil. Of those, 1,987 subjects (2.8%) met the inclusion criteria for FH diagnosis (age ≥18 and fasting LDL-c ≥190 mg/dL without statins or ≥160 mg/dL if on statin therapy). Of these, 200 individuals were randomly invited by phone to participate in the study in 2017. In addition to clinical and outpatient evaluations, questions about hypercholesterolemia, such as knowledge about FH, diagnosis, treatment adherence, cascade screening for FH in first-degree relatives and perception of CVD risk were investigated.

The majority of the participants were males, 95% had higher education and 12% had a previous event of CVD (myocardial infarction, angina, myocardial revascularization or stroke). In addition, the study identified that 97% of the participants were aware of having high cholesterol levels and, a significant percentage — 76% — reported having a first-degree relative with high cholesterol. However, only 4.5% (n=9) of the participants had their relatives called to check serum cholesterol levels. Analyzing the results above, it is reasonable to suggest that family screening does not seem to be carried out broadly and effectively.

Still regarding the perception of the hypercholesterolemia condition for the occurrence of CVD, only 18% of the participants recognized the condition of hypertension as a risk factor for CVD. On the other hand, 71% of the participants considered diabetes mellitus as the most relevant risk factor for CVD. These findings denote the minor importance given to hypercholesterolemia as a risk factor for CVD in the Brazilian population analyzed.

Reinforcing the lack of knowledge of hypercholesterolemia as an important risk factor for CVD, although a little more than 2/3 of the participants had regular consultations, only 1/3 reported knowledge about their recommended LDL-c. In individuals with suspected FH, a small number (24.5%) had heard of FH. The mean age of the participants suspected with FH diagnosis was 35, revealing the lack of early screening. Genetic diagnosis had been established for only 17% of the participants and only 4% had heard of xanthoma.

Keywords

Cardiovascular Diseases/mortality; Atherosclerosis; Risk Factors; Early Diagnosis; Lipid Metabolism Disorders; Hyperlipoproteinemia Type II.

Mailing Address: Elizabeth do Nascimento •
Departamento de Nutrição, Programa de Pós-Graduação em Nutrição - Universidade Federal de Pernambuco, Recife, PE – Brazil
E-mail: nlizbeth@gmail.com, nlizbeth01@hotmail.com

DOI: https://doi.org/10.36660/abc.20210168

The study represents a relevant contribution to the Brazilian population as there is a lack of studies conducted in Brazil assessing the knowledge of patients about the implications of hypercholesterolemia for the development of CVD. It should be noted that the subjects evaluated had a high social and educational level, which increases the importance of knowledge and attention to FH among the general public. The study data demonstrates that Brazilians need more information about FH and mass education campaigns need to be conducted on the risk of FH in the development of CVD and mortality.

References

1. Lozano R, Naghavi M, Foreman K, Lim S, Shibuya K, Aboyans V,et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2095-128.
2. World Health Organization (WHO). World Heart Day. Scale up prevention of heart attack and stroke, 2017 https://www.who.int/cardiovascular_diseases/world-heart-day/, 2017.
3. Faludi AA, Izar MC, Saraiva JF, Chacra AP, Bianco HT, Afiune Neto A, et al. Atualização da Diretriz Brasileira de Dislipidemias e Prevenção da Aterosclerose – 2017. Arq Bras Cardiol, 2017. 109(2 Supl 1):1-76.
4. Santos RD, Gagliardi AC, Xavier HT, Casella Filho A, Araújo DB, Cesena FY, et al. [First Brazilian Guidelines for Familial Hypercholesterolemia]. Arq Bras Cardiol. 2012;99(2 Suppl 2):1-28.
5. Civeira F. Guidelines for the diagnosis and management of heterozygous familial hypercholesterolemia. Atherosclerosis. 2004;173(1):55-68.
6. Motulsky AG. Genetic aspects of familial hypercholesterolemia and its diagnosis. Arteriosclerosis. 1989;9(1 Suppl):I3-7.
7. Soria LF, Ludwig EH, Clarke HR, Vega GL, Grundy SM, McCarthy BJ. Association between a specific apolipoprotein B mutation and familial defective apolipoprotein B-100. Proc Natl Acad Sci U S A. 1989;86(2):587-91.
8. Pamplona-Cunha H, Medeiros MF, Sincero TC, Back IC, Silva EL. Compound Heterozygous Familial Hypercholesterolemia Caused by LDLR Variants. Arq Bras Cardiol. 2020;115(3):587-9.
9. Pereira C, miname M, Makdisse M, Kalil Fo R, santos RD. Association of peripheral arterial and cardiovascular diseases in familial hypercholesterolemia. Arq Bras Cardiol. 2014;103(2):118-23.
10. Santos RD, Pereira C, Cesena F, Laurinavicius AG, Tabone V, Bittencourt MS. Cardiovascular Risk Misperception and Low Awareness of Familial Hypercholesterolemia in Individuals with Severe Hypercholesterolemia. Arq Bras Cardiol. 2021; 116(4):706-712.

Original Article

Worsening Renal Function and Congestion in Patients with Acute Heart Failure: A Study with Bioelectrical Impedance Vector Analysis (BIVA) and Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Humberto Villacorta,[1] Aline Sterque Villacorta,[1] Leonardo Simões de Castro Villacorta,[1] Analucia Rampazzo Xavier,[1] Salim Kanaan,[1] Felipe Mafort Rohen,[1] Leonardo Dinis Albuquerque,[1] Daniele Dantas Bastilho,[1] Cecília de Oliveira Cudischevitch[1]

Universidade Federal Fluminense,[1] Niterói, RJ - Brazil

Abstract

Background: **Worsening renal function (WRF) is frequently observed in the setting of aggressive diuresis for the treatment of acute decompensated heart failure (ADHF) and is associated with poor outcomes in some studies.**

Objective: **We sought to assess the relationship of WRF and congestion at discharge with events (cardiac death or heart failure hospitalization).**

Methods: **Eighty patients with ADHF were studied. WRF was defined by an absolute increase in serum creatinine of ≥0.5 mg/dL from the values measured at the time of admission. B-type natriuretic peptide (BNP) and plasma neutrophil gelatinase-associated lipocalin (NGAL) were measured at admission and at discharge. Congestive state at discharge was assessed using bioelectrical impedance vector analysis (BIVA). Primary endpoint was time to first event defined as a combination of cardiac death or heart failure hospitalization. Receiver operating characteristic (ROC) curve analysis was used to determine the best hydration index cutoff to predict events. Kaplan-Meier event-free survival curves were constructed and compared using the log-rank test. Cox proportional hazards models were used to investigate the association with events. The criterion for determining statistical significance was $p<0.05$.**

Results: **Mean age was 60.6±15 years, and 48 (60%) were male. Mean ejection fraction was 35.3±7.8%. WRF occurred in 37.5% of the sample. Baseline creatinine was associated with WRF ($p<0.001$), but neither admission BNP ($p=0.35$) nor admission NGAL ($p=0.18$) was predictor of WRF. Using Cox proportional hazard models, hydration index at discharge calculated with BIVA was significantly associated with events (HR 1.39, 95% CI 1.25-1.54, $p<0.0001$) but not WRF (HR 2.14, 95% CI 0.62-7.35, $p=0.22$).**

Conclusion: **Persistent congestion at discharge was associated with worse outcomes. WRF seems to be related to hemodynamic changes during the decongestion process but not to kidney tubular injuries. (Arq Bras Cardiol. 2021; 116(4):715-724)**

Keywords: **Heart Failure; Renal Insufficiency; Diuretics/therapeutic use; Electric Impedance; Hemodynamic; Mortality; Hospitalization; Patient Discharge.**

Introduction

Worsening renal function (WRF) is frequently observed in the setting of aggressive diuresis for the treatment of acute decompensated heart failure (ADHF) and is associated with poor outcomes in retrospective studies.[1] However, opposite findings have been observed in other studies;[2,3] and some studies have suggested that congestion rather than low cardiac output is related to renal dysfunction in heart failure (HF).[4-6] Additionally, some authors have shown that persistent congestion at discharge, irrespectively of WRF, is associated with worse outcomes.[7,8] However, these studies assessed congestion based on clinical signs.

New technologies can assess total body water more objectively, using tissue impedance analysis. Using bioelectrical impedance vector analysis (BIVA),[9] our group together with other centers, has previously shown that almost one third of ADHF patients are discharged with persistent congestion, including subclinical congestion, and that these patients have high 90-day mortality. The relationship of WRF and congestion evaluated by BIVA has never been studied. The use of this technology, by detecting subclinical congestion, could increase the accuracy of congestion evaluation and improve the prediction of events.

The mechanism of WRF after aggressive diuresis is poorly understood. There is doubt whether it is a result of renal tubular injury or just a reflection of hemodynamic changes occurring during the treatment of ADHF. Although creatinine

Mailing Address: Humberto Villacorta •
Universidade Federal Fluminense - Rua Marquês do Paraná, 303. Postal Code 24070-035, Divisão de Cardiologia, Niterói, RJ - Brazil
E-mail: huvillacorta@globo.com
Manuscript received July 12, 2019, revised manuscript November 11, 2019, acepted November 26, 2019

DOI: https://doi.org/10.36660/abc.20190465

is currently the standard biomarker for renal function, it has a delayed increase after kidney injury. Furthermore, WRF in ADHF, indicated by a rise in creatinine, may not reflect acute kidney injury and may not be prognostic in all patients.[2,3,7] Neutrophil gelatinase-associated lipocalin (NGAL) is a kidney tubular injury biomarker that can be measured in urine and plasma, and has been shown to predict acute kidney injury more precisely than creatinine.[10-12]

Therefore, the aim of this investigation was to assess the relationship of WRF and persistent congestion at discharge as assessed by BIVA in the prediction of long-term events, and to evaluate whether kidney tubular injury, assessed by plasma NGAL, is associated with WRF during the treatment of ADHF and with prognosis after discharge.

Methods

Patients

The study comprised 80 consecutive patients aged ≥18 years old, hospitalized in a university hospital for ADHF. The inclusion criteria were: 1) signs or symptoms of ADHF; 2) B-type natriuretic peptide (BNP) >100 pg/mL at admission; and 3) ejection fraction <50% as assessed by echocardiography. Patients were excluded if: 1) acute coronary syndrome as the main cause of current ADHF episode; 2) they were already on dialysis before enrollment or if dialysis initiation was planned during the current hospitalization. Patients were treated according to HF guidelines, and treatment decisions were left to the discretion of the physicians in charge. Patients who died on or before discharge from the initial hospitalization were excluded from the analyses. Each patient could only contribute once to the database, and, in case of multiple admissions, the first hospitalization occurring in the period under review was considered in this analysis. Figure 1 depicts the study flowchart.

Our study complies with the Brazilian National Council on Ethics in Human Research (CONEP) recommendations and was approved by the Ethics Committee of our hospital. Informed consent was requested and obtained from each patient recruited before entry into the study.

Measurements

Each patient underwent a complete clinical and laboratory examination at admission and during hospitalization. Serum creatinine levels were assessed and recorded daily from the time of admission until discharge. A Doppler echocardiogram to evaluate the systolic left ventricular (LV) function was performed during hospitalization.

BNP levels were measured in whole blood using the Triage® system (Alere Inc, San Diego, CA, USA), within six hours after collection at admission and at discharge. Plasma NGAL was assessed by the Triage NGAL Test (Alere Inc, San Diego, CA, USA), an immunoassay in a single-use plastic cartridge that contains a fluorescently labeled monoclonal antibody against NGAL labeled with a fluorescent dye and NGAL. There are built-in control features, including control immunoassays, to ensure that the test performs properly and that the reagents are functionally active. Several drops of whole blood or plasma are added to the sample port on

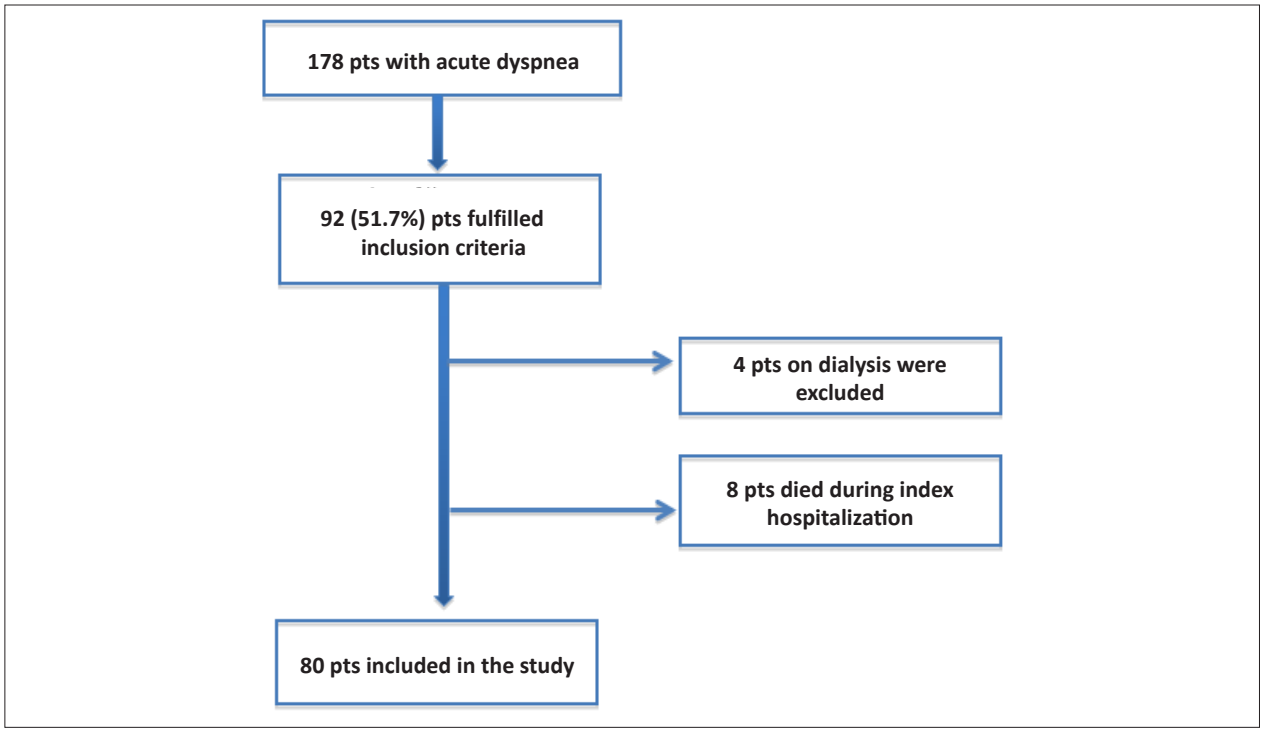


Figure 1 – *Study flowchart.*

the test device, and after this, the cells are automatically separated from the plasma via a filter. The sample reacts with fluorescent antibody conjugates within the reaction chamber and flows down the device detection lane by capillary action. The fluorescent antibody conjugates are captured on discrete solid-phase zones resulting in binding immunoassays that are specific for NGAL or the control antigens. Plasma NGAL of all patients was analyzed at admission and at discharge.

The BIVA method was used to assess total body water. This method utilizes the EFG Renal software (Akern, Pontassieve, Florence, Italy) for estimating the parameters of resistance, reactance, and phase angle. Then, the hydration index (HI) is calculated to estimate total body water. The normal HI range is 72.7% to 74.3%; values above this indicate congestion, and values below this cutoff indicate dehydration. BIVA was performed within 24 h before discharge by an independent investigator. Of note, the test is not operator-dependent and, therefore, there is no intra- or interobserver variability. The machine rejects the test in case of poor signal quality. Figure 2 shows the BIVA machine and the application of electrodes on patients' hand and foot.

Definitions

ADHF was defined as one or more signs or symptoms of HF, including dyspnea on exertion, rales or crackles, gallop heart rhythm, jugular venous distention, orthopnea, paroxysmal nocturnal dyspnea, use of more than two pillows to sleep, fatigue, edema, frequent coughing, a cough that produces mucous or blood-tinged sputum, or a dry cough when lying flat.

WRF was defined by an absolute increase in serum creatinine of ≥0.5 mg/dL from the values measured at the time of admission. Congestion at discharge was defined as HI >74.3%. Patients with no signs of congestion on physical examination and HI >74.3% were considered as having subclinical congestion. For survival analysis, patients were divided into four subgroups, based on the detection of WRF during hospitalization and the presence or not of congestion at the time of discharge, as follows: no WRF and no congestion (no WRF/no congestion), WRF in the absence of congestion (WRF/no congestion), no WRF and congestion (no WRF/no congestion), and presence of both WRF and congestion (WRF/congestion). A history of chronic kidney disease was defined

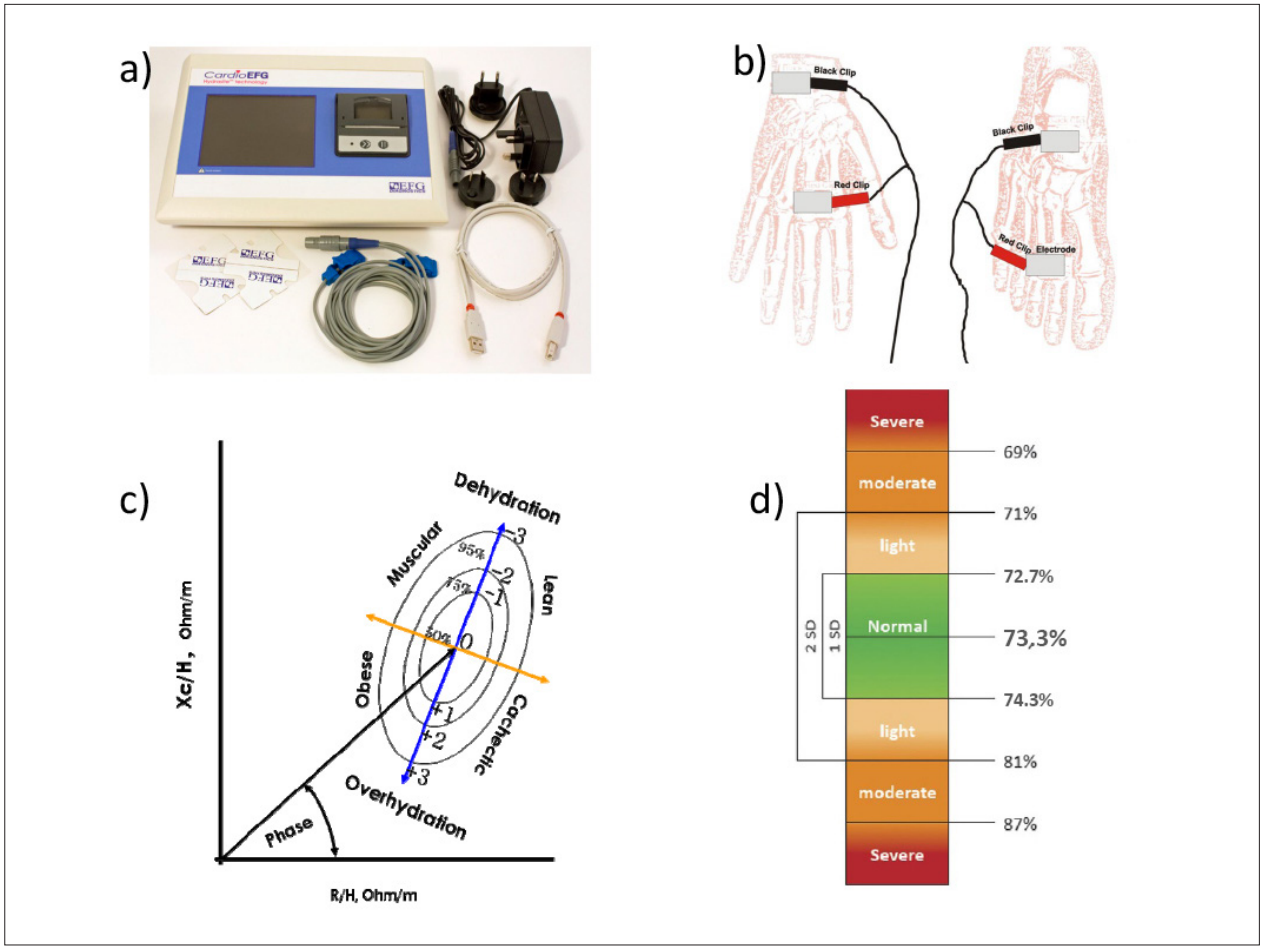


Figure 2 – *Bioelectrical impedance vector analysis (BIVA). a) The BIVA machine; b) the electrodes are placed on the patient's right hand and foot; c) vector analysis: the signs are captured for a few seconds and after analysis, according to the phase angle formed by the vector, the degree of hydration is estimated; d) degree of hydration according to the hydration index*

based on a history of an estimated glomerular filtration rate <60 mL/min per 1.73 m^2.

Follow-up and Endpoints

Patients were followed-up at our Heart Failure Clinic and visits took place at 3-month intervals. Telephone contacts to assess vital status were made whenever necessary. No patient was lost to follow-up and mean follow-up was 234±174 days. Primary endpoint was time to first event defined as a combination of cardiac death or HF hospitalization.

Hospitalization was defined as any unplanned admission to hospital, which required an overnight stay. Hospitalizations were classified as caused by HF when they were caused by worsening symptoms of HF, with signs of fluid overload, requiring intravenous furosemide treatment.

Statistical Analysis

Subjects were recruited by convenience sampling. Data are presented as mean ± standard deviation (SD), except for BNP, NGAL, and creatinine, for which median and interquartile ranges are provided. Categorical variables were analyzed using the chi-square test. For comparison of numerical data, Student's t test for independent samples or the Mann-Whitney test (non-parametric) was used. The homogeneity of the variance was tested by the Levene test. Non-parametric methods were used, since some variables did not present normal distribution, due to the great dispersion and rejection of the normality hypothesis according to the Kolmogorov-Smirnov test. Receiver operating characteristic (ROC) curve analysis was used to determine the best HI cutoff to predict events. Kaplan-Meier event-free survival curves were constructed and compared using the log-rank test. Cox proportional hazards models were used to investigate the prospective association of WRF and persistent congestion with events during follow-up. Independent variables included in the model were age, gender, IH, WRF and creatinine, BNP, and NGAL at discharge. The criterion for determining statistical significance was 5%. Statistical analysis was performed by MedCalc® statistical software, version 14.12.0 (Ostend, Belgium).

Results

Mean age was 60.6±15.0 years and 48 (60%) were male. Mean left ventricular ejection fraction was 35±7.8%. WRF occurred in 37.5% of the sample. The characteristics of the patients with and without WRF are shown in Table 1. HF etiologies were ischemic cardiomyopathy in 23 (28,7%), hypertension in 42 (52,5%), idiopathic cardiomyopathy in 10 (12,5%), alcoholic cardiomyopathy in 3 (3,7%), and chemotherapy in 2 (2,6%). Creatinine and HI at admission were higher and serum sodium was lower in the WRF group. Neither BNP nor NGAL were statistically different in patients with or without WRF. Median length of stay (LOS) was eight days (interquartile range 7-12 days). At discharge, creatinine was higher in the WRF group, and HI was slightly higher in patients with WRF but this did not reach statistical difference.

Median peak creatinine in the WRF group was 2.1 mg/dL (interquartile range 1.82-2.48). BNP dropped from admission to discharge in both WRF [806 (531-1276) vs. 455 (340-749) pg/mL, p<0.0001] and no WRF group [667.5 (478-1255) vs. 404 (268-661) pg/mL, p<0.0001]. NGAL also dropped from admission to discharge in both groups [WRF 249.5 (128-539) vs. 164.5 (116-286) pg/mL, p<0.0001; no WRF 216 (92-352) vs. 190 (98-312) pg/mL, p=0.0001]. Mean LOS was 8.3±3.1 days in the no WRF/ no congestion group, 11.4±5.3 days in WRF/no congestion, 12.0±4.8 days in no WRF/congestion and 12.5±4.0 days in the WRF/congestion group (p=0.019). Mean delta from admission to discharge of HI in these four groups were, respectively, 8.4±2.4%, 8.0±2.5%, 5.3±2.6% and 5.1±2.1% (p=0.0002).

During follow-up, 27 (33,7%) events were observed (7 deaths and 20 hospitalizations). Characteristics of patients with and without events are depicted in Table 2. The number of events in each group is shown in Table 3. Figure 3 shows the Kaplan-Meyer survival curves for the four groups according to the presence of WRF and persistent congestion at discharge. As observed, patients with persistent congestion regardless of WRF during hospitalization had the worst prognosis. Patients with both WRF and persistent congestion had a hazard ratio for death or readmission for HF 9.1 times (95% CI, 1.41-58.5) of that in the 'WRF/no congestion' group and 27.4 times (95% CI, 4.5-164.4) of that in the 'no WRF/no congestion' group. Using Cox proportional hazards regression analysis, male gender and HI were independent predictors of the primary endpoint (Table 4). Figure 4 shows mean creatinine levels at admission, mean peak, and at discharge in patients with and without events. Patients with events had significantly higher values of creatinine in all comparisons.

Discussion

The main findings of our study are that the presence of WRF alone during HF hospitalization is not associated with worse outcomes after discharge. On the other hand, persistent congestion at discharge is a strong predictor of events, especially in patients with WRF during hospitalization.

At admission, the variables associated with WRF were creatinine, blood urea nitrogen (BUN), serum sodium, and HI. The association between higher creatinine at admission and WRF is probably explained by congestion. Low serum sodium and high HI support this hypothesis. Congestion impairs glomerular filtration and may result in elevation of creatinine.

Initial studies suggested that any worsening of renal function in patients with acute HF was related to a worse prognosis.[1] However, some studies, with opposite results, led to the questioning of this concept.[2,3,7] Testani et al.[2] evaluated the relationship of hemoconcentration, WRF, and outcomes in patients submitted to aggressive decongestion during the treatment of ADHF. They found that hemoconcentration was significantly associated with more aggressive fluid removal and deterioration in renal function. However, patients with hemoconcentration had improved survival suggesting that aggressive decongestion, even in the setting of WRF, can positively affect survival.

The relationship of congestion at discharge, WRF, and worse outcomes has already been demonstrated in previous studies. However, the diagnosis of congestion in these studies

Table 1 – Characteristics of patients with and without worsening renal function

Variables	WRF n=30	No WRF n=50	p value
Age (y)	59.9±17.8	61±13.4	0.75
Male gender	17 (56.7%)	31 (62%)	0.44
Ischemic aetiology	8 (26.7%)	15 (30%)	0.75
History of diabetes	11 (36.6%)	17 (34%)	0.81
History of hypertension	22 (73.3%)	34 (68%)	0.61
History of COPD	5 (16.6%)	8 (16%)	0.94
Atrial fibrillation	6 (20%)	11 (22%)	0.83
Chronic kidney disease	13 (43.3%)	16 (32%)	0.31
Heart rate (bpm)	72.4±8.2	72.7±7.8	0.84
Systolic blood pressure (mmHg)	110.3±13.4	110.6±15.5	0.94
Diastolic blood pressure (mmHg)	69.5±9.8	71.5±9.7	0.37
LV ejection fraction (%)	36.7±6	34.5±8.6	0.19
Laboratory characteristics			
Creatinine (mg/dL)			
Admission	1.45 (1.19-1.84)	1.05 (0.91-1.2)	<0.0001
Peak	2.1 (1.82-2.48)	1.22 (1.13-1.38)	<0.0001
Discharge	1.5 (1.26-1.8)	1.0 (0.87-1.13)	<0.0001
BUN (mg/dL)			
Admission	42.4 (23.4-61)	31.4 (18-39.3)	0.007
Discharge	39.6 (21.5-58.4)	30.2 (17.4-36.4)	0.02
BNP (pg/mL)			
Admission	806 (531-1276)	667.5 (478-1255)	0.35
Discharge	455 (340-749)	404 (268-661)	0.12
NGAL (pg/mL)			
Admission	249.5 (128-539)	216 (92-352)	0.18
Discharge	164.5 (116-286)	190 (98-312)	0.82
Serum Sodium (mEq/L)			
Admission	135±4.1	137.6±3.2	0.002
Discharge	137.4±3.9	137.5±3.6	0.93
Hydration index (BIVA) %			
Admission	81.3±3.4	78.2±3.2	0.0001
Discharge	77.9±5.8	75.8±4.6	0.08
Medications at discharge			
Betablockers	29 (96.6%)	48 (98%)	0.70
ACE inhibitors	25 (83.3%)	41 (82%)	0.88
Angiotensin receptor blockers	4 (13.3%)	8 (16%)	0.74
Spironolactone	17 (56.7%)	31 (62%)	0.64
Furosemide	29 (96.6%)	47 (94%)	0.60
Digoxin	2 (6.7%)	4 (8%)	0.83

BIVA: bioelectrical impedance vector analysis; BNP: B-type natriuretic peptide; BUN: blood urea nitrogen; COPD: chronic obstructive pulmonary disease; LV: left ventricular; NGAL: Neutrophil gelatinase-associated lipocalin; ACE: angiotensin converting enzyme; WRF: worsening renal function.

Table 2 – Characteristics of the patients with and without events

Variables	Events n=27	No events n=53	p value
Age (y)	61.6±13.7	60.2±15.9	0.68
Male gender	21 (77.8%)	27 (51%)	0.021
Ischemic aetiology	9 (33.3%)	14 (26%)	0.47
History of diabetes	10 (37%)	16 (30.2%)	0.46
History of hypertension	20 (74%)	36 (67.9%)	0.43
History of COPD	5 (18.5%)	8 (15%)	0.30
Atrial fibrillation	7 (26%)	10 (18.8%)	0.47
Chronic kidney disease	10 (37%)	19 (35.8%)	0.91
Heart rate (bpm)	71.4±8.2	73.3±7.7	0.32
Systolic blood pressure (mmHg)	113.8±17.7	108.8±12.6	0.19
Diastolic blood pressure (mmHg)	71.4±11	70.5±9.1	0.69
LV ejection fraction (%)	34.9±7.5	35.6±8	0.68
Laboratory characteristics			
Creatinine (mg/dL)			
Admission	1.29 (1.1-1.76)	1.1 (0.91-1.29)	0.002
Peak	1.9 (1.40-2.34)	1.3 (1.16-1.75)	0.001
Discharge	1.21 (1.1-1.8)	1.0 (0.88-1.33)	0.003
BUN (mg/dL)			
Admission	40.3 (20.4-64)	30.2 (16-35.3)	0.005
Discharge	37.2 (22.3-57.4)	31.4 (15.5-34.2)	0.10
BNP (pg/mL)			
Admission	921 (685-1689)	602 (487-964)	0.015
Discharge	580 (390-1210)	377 (277-605)	0.007
NGAL (pg/mL)			
Admission	275 (156-478)	187 (100-341)	0.06
Discharge	214 (138-430)	168 (85-312)	0.035
Serum Sodium (mEq/L)			
Admission	135±5.1	137.3±3.4	0.018
Discharge	136.4±4.9	138.5±3.2	0.023
Hydration index (BIVA) %			
Admission	84.6±3.6	79.2±4.2	<0.0001
Discharge	82.2±4.8	73.7±2.0	<0.0001
WRF	15 (55.6%)	15 (28.3%)	0.017

BIVA: bioelectrical impedance vector analysis; BNP: B-type natriuretic peptide; BUN: blood urea nitrogen; COPD: chronic obstructive pulmonary disease; LV: left ventricle; NGAL: Neutrophil gelatinase-associated lipocalin; WRF: worsening renal function.

Table 3 – Number of events in the four groups according to the presence or not of worsening of renal function and congestion

Events	No WRF/No congestion n=42	WRF/No congestion n=21	No WRF/Congestion n=8	WRF/Congestion n=9
Death	0	3 (14.3%)	2 (25%)	2 (22.2%)
Hospitalization	5 (12%)	3 (14.3%)	6 (75%)	7 (77.7%)
Total	5 (12%)	6 (28.6%)	8 (100%)	9 (100%)

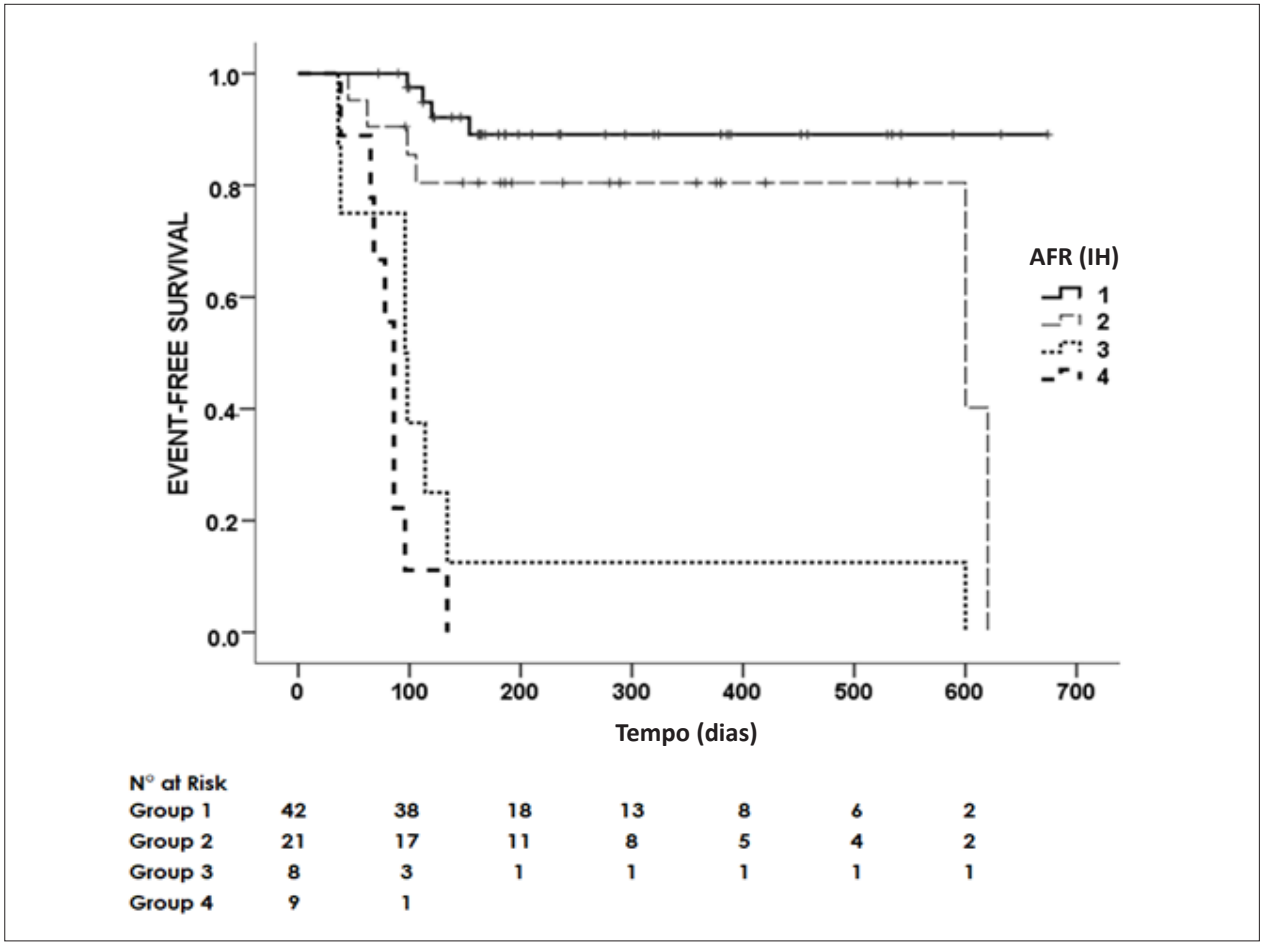


Figure 3 – *Event-free survival rate based on the detection of WRF during hospitalization and the presence or not of congestion at the time of discharge. 1= No WRF/No congestion; 2= WRF/No congestion; 3= No WRF/Congestion; and 4= WRF/Congestion. Time is depicted as days (p<0.001); Congestion was assessed by hydration index (HI) with bioelectrical impedance vector analysis (BIVA); WRF: worsening renal function.*

was based only on clinical signs.[7,8] The novel finding in our study is that we used an objective assessment of congestion with BIVA. We were able to demonstrate that even subclinical congestion, as detected with this technology, negatively affects survival and readmissions. Using BIVA we have previously demonstrated that some patients with ADHF are discharged with overt or subclinical congestion and this was related to worse outcomes.[9] Now we confirm this finding and add information on the relationship of congestion and WRF. In the present study, a HI >76.5% at discharge was predictive of events. This cutoff includes subclinical congestion and may have increased the sensisivity to detect events.

Several studies have shown that congestion, but not low output is associated with WRF.[4-6,13-16] In an analysis of the ADHERE (Acute Decompensated Heart Failure National Registry) database, of 118,465 HF admissions, a relationship between left ventricular systolic dysfunction and renal impairment could not be demonstrated.[14] Moreover, an analysis of the ESCAPE (Evaluation Study of Congestive Heart

Table 4 – Cox proportional hazards models to investigate the independent association of worsening of renal function and persistent congestion with events during follow-up

Variable	HR	95% CI	p value
Age	1.02	0.98-1.06	0.25
Gender	3.31	1.04-10.5	0.04
Creatinine	1.08	0.23-4.98	0.91
NGAL	0.99	0.99-1.00	0.51
BNP	0.99	0.99-1.00	0.10
Hydration*	1.39	1.25-1.54	<0.0001
WRF	2.14	0.62-7.35	0.22

*BNP:B-type natriuretic peptide; HR:hazard ratio; NGAL:Neutrophil gelatinase-associated lipocalin; *estimated by bioelectrical impedance vector analysis (BIVA); WRF: worsening renal function.*

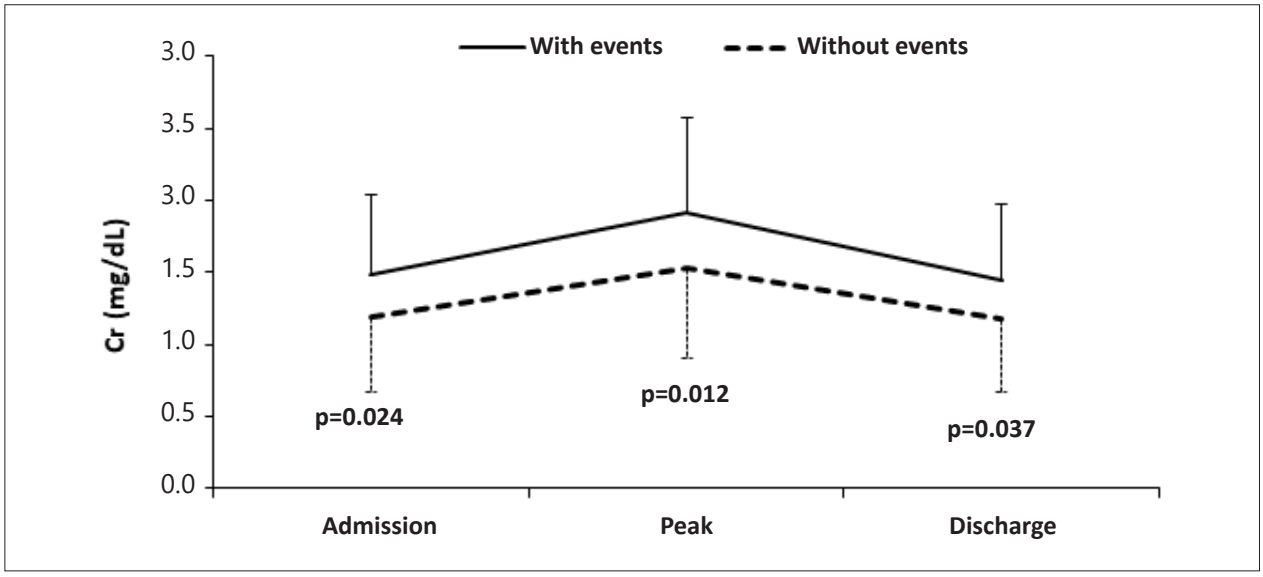


Figure 4 – *Mean creatinine (Cr) at admission, peak creatinine, and discharge creatinine in patients with and without events. Bars are standard deviation. P values refer to intergroup comparisons (Students' t-test).*

Failure and Pulmonary Artery Catheterization Effectiveness) database, the authors found that in decompensated HF patients, kidney function did not correlate with cardiac index, pulmonary capillary wedge pressure, or systemic vascular resistance, but rather was with right atrial pressure.

Congestion can lead to WRF through several mechanisms.[4-6,13-16] Kidney venous congestion directly impairs glomerular filtration rate.[13] Additionally, many abdominal pathways can lead to WRF.[13] For instance, increased intra-abdominal pressure, as a marker of extreme abdominal congestion, is correlated with renal dysfunction in patients with severe HF.[13] Moreover, alterations in spleen and liver contribute to congestion and renal dysfunction.[13] Finally, gut-derived hormones might influence sodium homeostasis, whereas entrance of bowel toxins into the circulatory system, as a result of impaired intestinal barrier function secondary to congestion, might further depress cardiac and renal function.[13,17]

Based on these findings, aggressive treatment of congestion has been proposed as the mainstay treatment of WRF in the setting of ADHF.[18-20] In one study,[18] a protocol with intensification of diuretic treatment in patients with WRF and ADHF resulted in a greater weight change and greater net fluid loss after 24 hours as compared with standard treatment, with a slight improvement in renal function.[18]

We found no relationship between admission NGAL and WRF nor between discharge NGAL and outcomes. Our results are in accordance with the study by Ahmed et al.[21] who found no correlations between validated tubular injury biomarkers (NGAL, NAG, and KIM-1) with WRF in patients with ADHF undergoing aggressive diuresis. Of note, increases in such biomarkers were paradoxically associated with improved survival.[21] Taken together, these findings suggest that congestion is a major contributor to WRF in ADHF, and if aggressive decongestion is promoted, WRF has no adverse impact on outcomes.

However, the present study has some limitations. First, this is a single-center study and caution is advised when extending the findings to other populations. Second, the number of patients in the present study is relatively small.

Conclusion

In conclusion, using BIVA to assess the hydration state at discharge, we demonstrated that persistent congestion but not WRF is associated with worse outcomes in patients hospitalized for ADHF. Additionally, we found that WRF seems to be related to congestion and to hemodynamic changes during the decongestion process but not to kidney tubular injuries, since no relationship was found between NGAL, WRF, and outcomes.

Author Contributions

Conception and design of the research and Statistical analysis: Villacorta H; Acquisition of data: Villacorta H, Villacorta AS, Villacorta LSC, Xavier AR, Kanaan S, Rohen FM, Albuquerque LD, Bastilho DD, Cudischevitch CO; Analysis and interpretation of the data: Villacorta H, Villacorta AS, Villacorta LSC, Xavier AR, Kanaan S, Bastilho DD; Writing of the manuscript: Villacorta H, Xavier AR; Critical revision of the manuscript for intellectual content: Villacorta H, Villacorta AS, Villacorta LSC, Kanaan S, Rohen FM, Albuquerque LD, Bastilho DD, Cudischevitch CO.

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.

References

1. Gottlieb SS, Abraham W, Butler J, Forman DE, Loh E, Massie BM, et al. The prognostic importance of different definitions of worsening renal function in congestive heart failure. J Card Fail. 2002;8(3):136-41.
2. Testani MJ, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation. 2010;122(3):265-72.
3. Aronson D, Burger AJ. The relationship between transient and persistent worsening renal function and mortality in patients with acute decompensated heart failure. J Card Fail. 2010;16(7):541-7.
4. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol .2009;53(7):589-96.
5. Damman K, van Deursen VM, Navis G, Voors AA, van Veldhuisen DJ, Hillege HL. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol. 2009;53(7):582-8.
6. Guglin M, Rivero A, Matar F, Garcia M. Renal dysfunction in heart failure is due to congestion but not low output. Clin Cardiol. 2011;34(2):113-6.
7. Metra M, Davison B, Bettari L, Sun H, Edwards C, Lazzarini V, et al. Is worsening renal function an ominous prognostic sign in patients with acute heart failure? The role of congestion and its interaction with renal function. Circ Heart Fail. 2012;5(1):54-62.
8. Wattad M, Darawsha W, Solomonica A, Hijazi M, Kaplan M, Makhoul BF, et al. Interaction between worsening renal function and persistent congestion in acute decompensated heart failure. Am J Cardiol. 2012;115:932-7.
9. Santarelli S, Russo V, Lalle I, De Berardinis B, Navarin S, Magrini L, et al. Usefulness of combining admission brain natriuretic peptide (BNP) plus hospital discharge bioelectrical impedance vector analysis (BIVA) in predicting 90-day cardiovascular mortality in patients with acute heart failure. Intern Emerg Med. 2017;12(4):445-51.
10. Bolignano D, Donato V, Coppolino G, Campo S, Buemi A, Lacquaniti A, et al. Neutrophil gelatinase-associated lipocalin (NGAL) as a marker of kidney damage. Am J Kidney Dis. 2008;52(3):595-605.
11. Zhou F, Luo Q, Wang L, Han L. Diagnostic value of neutrophil gelatinase-associated lipocalin for early diagnosis of cardiac surgery-associated acute kidney injury: a meta-analysis. Eur J Cardiothorac Surg .2016;49(3):746-55.
12. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A, for the NGAL Meta-analysis Investigator Group. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: a systematic review and meta-analysis. Am J Kidney Dis. 2009:54(6):1012-24.
13. Verbrugge FH, Dupont M, Streels P, Grieten L, Malbrain M, Tang WHW, et al. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. J Am Coll Cardiol 2013;62(6):485-95.
14. Heywood JT, Fonarow GC, Constanzo MR, Mathur VS, Wignesvaran JR, Wynne J. ADHERE Scientific Advisory Committee and Investigators. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: A report from the ADHERE database. J Card Fail. 2007;13(6):422-30.
15. Nohria A, Hasselblad V, Stebbins A, Pauly DF, Fonarow GC, Shah M, et al. Cardiorenal interactions: Insights from the ESCAPE trial. J Am Coll Cardiol 2008;51(13):1268-74.
16. Dammann K, Voors AA, Hillege HL, Navis G, Lechat P, van Veldhuisen DJ, et al. CIBIS-2 Investigators and Committee. Congestion in chronic systolic heart failure is related to renal dysfunction and increased mortality. Eur J Heart Fail .2010;12(9):974-82.
17. Sandek A, Bauditz J, Swidsinski A, Buhner S, Weber-Eibel J, von Haehling S, et al. Altered intestinal function in patients with chronic heart failure. J Am Coll Cardiol 2007;50(16):1561-9.
18. Grodin JL, Stevens SR, de Las Fuentes L, Kiernan M, Birati EY, Grupta D, et al. Intensification of medication therapy for cardiorenal syndrome in acute decompensated heart failure. J Card Fail .2016;22(1):26-32.
19. Onuigbo MAC, Agbasi M, Sengodan M, Rosario KF. Acute kidney injury in heart failure revisited. The ameliorating impact of "decongestive diuresis" on renal dysfunction in type 1 acute cardiorenal syndrome: Accelerated rising Pro B natriuretic peptide is a predictor of good renal prognosis. J Clin Med. 2017,6(9):82 doi:10.3390/jcm6090082.
20. Thind GS, Loehrke M, Wilt JL. Acute cardiorenal syndrome: mechanisms and clinical implications. Cleveland Clin J Med. 2018;85(3):231-9.
21. Ahmad T, Jackson K, Rao VS, Tang WHW, Brisco-Bacik MA, Chen HH, et al. Worsening renal function in acute heart failure patients undergoing aggressive diuresis is not associated with tubular injury. Circulation. 2018;137(19):2016-28.

Use of Diuretic Therapy in Patients with Decompensated Heart Failure and Acute Kidney Injury. What to do in this Dilemma?

Rafael Marques Calazans,[1] Mariana Bellaguarda de Castro Sepulvida,[1] Egli Belinazzi Quadrado,[1] Roberto Dischinger Miranda[1,2]

Seção Cardiovascular, Disciplina de Geriatria e Gerontologia, Escola Paulista de Medicina da Universidade Federal de São Paulo,[1] São Paulo, SP - Brazil
Hospital Israelita Albert Einstein,[2] São Paulo, SP - Brazil

Short Editorial related to the article: Worsening Renal Function and Congestion in Patients with Acute Heart Failure: A Study with Bioelectrical Impedance Vector Analysis (BIVA) and Neutrophil Gelatinase-Associated Lipocalin (NGAL)

Heart failure (HF) is a severe public health problem due to its high prevalence, morbidity and mortality.[1] It is the main cause of hospitalization in the United States.[2] The prevalence of the disease increases with age, making elderly patients even more susceptible to the repercussions of this disease.[1] This increases the importance of precise treatment of HF and its complications, including decompensated HF (dHF).

In patients with dHF, who require diuretic therapy, concomitant acute kidney injury (AKI) is a common finding. The big question when it comes to treatment with diuretics in situations where kidney function is altered is to know the reason for the dysfunction: Is the patient is still congested, requiring optimization of diuretic therapy (type I cardiorenal syndrome)? Or is it a patient whose diuretic therapy was carried out excessively, causing hypovolemia, which led to low renal perfusion (pre-renal AKI) or even an acute tubular necrosis?

This question gains a lot of importance in clinical practice because it implies diametrically opposed therapeutic approaches in both situations: intensifying diuretic therapy and discontinuing diuretics, or even initiating proper venous hydration. And the fact that these patients are often elderly, multicomorbid, in the context of concomitant infection, makes it clinically challenging to interpret the hemodynamic profile. It is hard to find an emergency or intensive care unit doctor that has never been faced with this dilemma.

Previous publications corroborate this issue, with some articles considering congestion as the major factor associated with worsening kidney injury in patients with dHF, indicating a more aggressive diuretic therapy,[3,4] while others recognize the potentially harmful effect of aggressive diuretic therapy, including hypovolemia, thus indicating a more cautious diuretic therapy,[5] especially in elderly patients[6] (Figure 1).

Keywords

Heart Failure/complications; Renal Insufficiency Chronic/complications; Mortality; Health Public; Aging; Hospitalization; Diuretics; Creatinine; Markers Biological; Lipocalins; Electric Impedance.

Mailing Address: Roberto Dischinger Miranda •
Av. Ibirapuera, 2.907/715. Postal Code 04029-200, São Paulo, SP - Brasil
E-mail: roberto.miranda@institutolongevita.com.br

DOI: https://doi.org/10.36660/abc.20210238

The laboratory and imaging methods commonly available to access the volume and hemodynamic profile are usually of little help in this regard, as there is no method considered to be the gold standard, nor are there any guidelines or protocols as to how best to answer this question. Methods commonly used in ICUs, such as variation in pulse pressure and assessment of collapsibility of superior and inferior vena cava, are validated only for responsiveness to the infusion of fluids and are of little help when it comes to fluid removal, and are only effective in mechanically ventilated patients. B-type natriuretic peptide (BNP) and N-terminal pro b-type natriuretic peptide (NT-ProBNP) plasma levels have a well-established importance in the diagnosis and prognosis of dHF. However, it has been little studied as a tool to access hemodynamic profile in these patients, with a study published showing poor performance.[7]

The article by Villacorta et al.,[8] reported in the current volume of Arquivos Brasileiros de Cardiologia[8], investigates whether the mechanism of worsening of renal function after aggressive diuretic treatment in patients with dHF occurs due to congestion or renal tubular injury. The article also assesses whether the presence of AKI during treatment or presence of congestion at discharge are predictors of outcome after an episode of dHF. Altogether, 85 patients were evaluated using NGAL as a marker for renal tubular injury and the hydration index with electrical bioimpedance to define the presence of congestion at discharge. It was found that persistent congestion, not AKI, is associated with worse outcomes in patients hospitalized for dHF; moreover, it showed that AKI was a consequence of congestion, rather than of a renal tubular injury.

The authors finish the article[8] by showing some publications in favor of aggressive diuretic therapy and conclude that, as long as aggressive reduction of congestion is promoted, AKI will not have any adverse impact on the outcomes.

The article[8] adds to the current view on the subject mainly in two ways. Firstly, for the simple fact that it discusses this very important and common theme in medical practice, but relatively little debated and studied. Secondly, for bringing some new ways of analyzing the issue, more precisely using NGAL, a marker of kidney injury that is faster and more accurate than creatinine, and the use of electrical bioimpedance to detect subclinical congestion, which would increase the accuracy of assessment and the ability to predict outcomes.

Despite this, because it is a complex issue that is hard to assess with the methods available in medical practice,

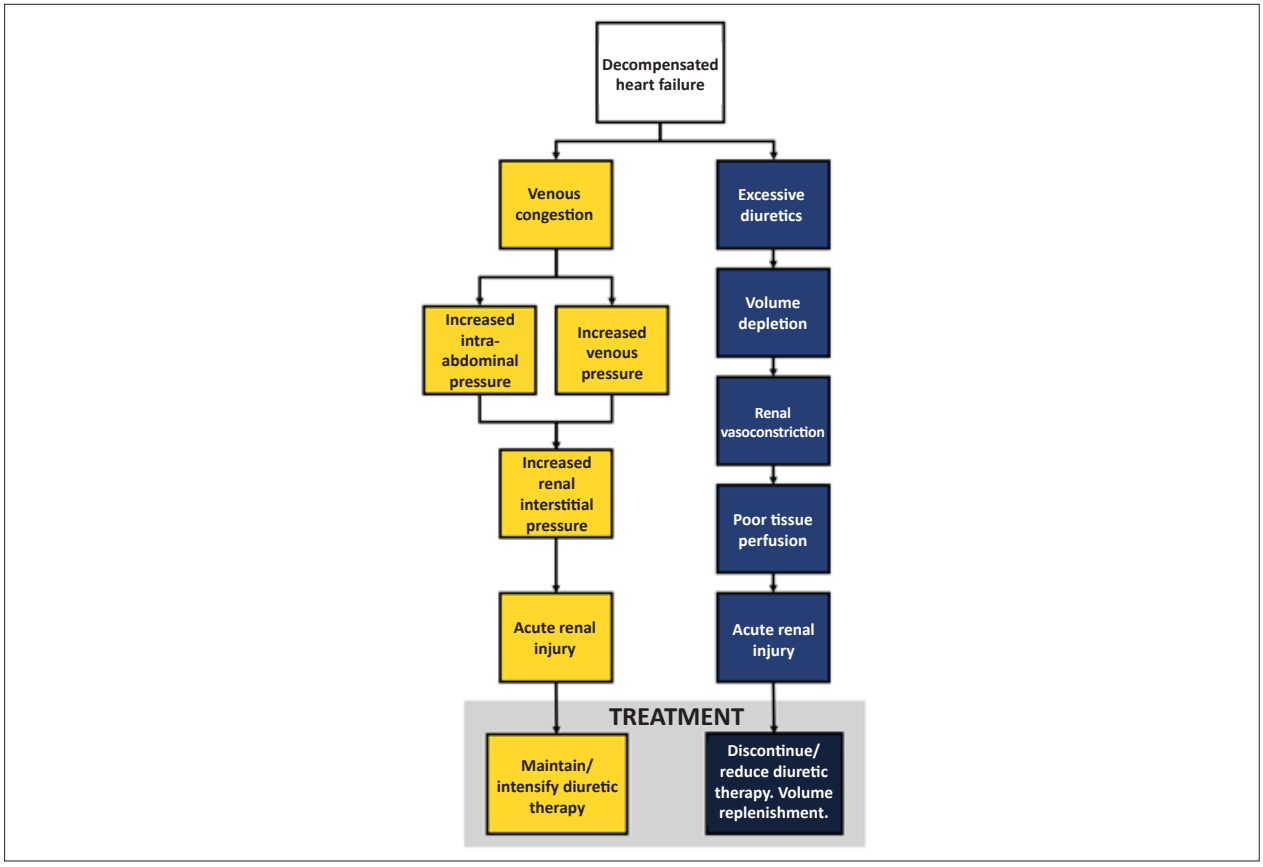


Figure 1 – *Schematic representation of the physiopathology and management of diuretic therapy of patients with decompensated heart failure under treatment.*

management of patients with AKI in the context of dHF remains a huge clinical challenge, with many questions and few definitive answers. Therefore, further studies are needed to help understand the subject. In the current scenario, the individualization of cases and the clinical perception of the evaluator are still critical.

References

1. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. Circulation. 2018;137(12):e67-492.
2. Heidenreich PA, Albert NM, Allen LA, Bluemke DA, Butler J, Fonarow GC, et al. Forecasting the impact of heart failure in the United States: a policy statement from the American Heart Association. Circ Heart Fail. 2013;6(3):606-19.
3. Testani JM, Chen J, McCauley BD, Kimmel SE, Shannon RP. Potential effects of aggressive decongestion during the treatment of decompensated heart failure on renal function and survival. Circulation. 2010;122(3):265-72.
4. Grodin JL, Stevens SR, Fuentes LL, Kiernan M, Birati EY, Gupta D, et al. Intensification of medication therapy for cardiorenal syndrome in acute decompensated heart failure. J Card Fail. 2016;22(1):26-32.
5. Butler J, Forman DE, Abraham WT, Gottlieb SS, Loh E, Massie BM, et al. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. Am Heart J. 2004;147(2):331-8.
6. Maeder MT, Rickli H, Pfisterer ME, Muzzarelli S, Ammann P, Fehr T, et al. Incidence, clinical predictors, and prognostic impact of worsening renal function in elderly patients with chronic heart failure on intensive medical therapy. Am Heart J. 2012;163(3):407-14.
7. Almeida Junior GLG, Clausll N, Garcia MI, Esporcatte R, Rangel FOD, Rocha RM, et al. Natriuretic peptide and clinical evaluation in the diagnosis of heart failure hemodynamic profile: comparison with tissue doppler echocardiography. Arq Bras Cardiol. 2018;110(3):270-7.
8. Villacorta H, Villacorta AS, Villacorta LSC, Xavier ALR, Kanaan S, Rohen FM, et al. Agravamento da Função Renal e Congestão em Pacientes com Insuficiência Cardíaca Aguda: Estudo com Análise Vetorial de Bioimpedância Elétrica (BIVA) e Lipocalina Associada à Gelatinase Neutrofílica (NGAL). Arq Bras Cardiol.2021; 116(4):715-724.

Carotid Artery Atherosclerotic Profile as Risk Predictor for Restenosis After Coronary Stenting

Cássia da Silva Antico Rodrigues,[1] Rodrigo Bazan,[1] Fabrício Moreira Reis,[1] Caroline F. S. Mazeto Pupo da Silveira,[1] Lívia Maria Severino Hueb,[1] Fábio Cardoso de Carvalho,[1] Hélio Rubens de Carvalho Nunes,[1] Katashi Okoshi,[1] João Carlos Hueb,[1] Silméia Garcia Zanati Bazan[1]

Universidade Estadual Paulista Julio de Mesquita Filho - Faculdade de Medicina Campus de Botucatu,[1] Botucatu, SP – Brazil

Abstract

Background: **The incidence of restenosis of the coronary artery after a bare-metal stent implant has been lower than in simple balloon angioplasty; however, it still shows relatively high rates.**

Objective: **The aim of this study was to find new risk indicators for in-stent restenosis using carotid ultrasonography, that, in addition to the already existing indicators, would help in decision-making for stent selection.**

Methods: **We carried out a cross-sectional prospective study including 121 consecutive patients with chronic coronary artery disease who had undergone percutaneous coronary intervention with repeat angiography in the previous 12 months. After all cases of in-stent restenosis were identified, patients underwent carotid ultrasonography to evaluate carotid intima-media thickness and atherosclerosis plaques. The data were analyzed by Cox multiple regression. The significance level was set a $p<0.05$.**

Results: **Median age of patients was 60 years (1st quartile = 55, 3rd quartile = 68), and 64.5% of patients were male. Coronary angiography showed that 57 patients (47.1%) presented in-stent restenosis. Fifty-five patients (45.5%) had echolucent atherosclerotic plaques in carotid arteries and 54.5% had echogenic plaques or no plaques. Of patients with who had echolucent plaques, 90.9% presented coronary in-stent restenosis. Of those who had echogenic plaques or no plaques, 10.6% presented in-stent restenosis. The presence of echolucent plaques in carotid arteries increased the risk of coronary in-stent restenosis by 8.21 times (RR=8.21; 95%CI: 3.58-18.82; $p<0.001$).**

Conclusions: **The presence of echolucent atherosclerotic plaques in carotid artery constitutes a risk predictor of coronary in-stent restenosis and should be considered in the selection of the type of stent to be used in coronary angioplasty. (Arq Bras Cardiol. 2021; 116(4):727-733)**

Keywords: **Coronary Artery Disease; Atherosclerosis; Coronary restenosis; Stents; Angioplasty, Balloon, Coronary; Carotid Arteries/ultrasonography; Plaque, Atherosclerotic.**

Introduction

The development of bare-metal stents (BMS) was a great advance in balloon angioplasty for treating symptomatic coronary artery disease. With the use of stents, restenosis can be avoided by attenuating the elastic recoil and promoting a negative geometric remodeling, resulting in reduction of vessel lumen.[1] However, the need for new revascularizations due to in-stent restenosis was still relatively high, occurring in 10% to 20% of patients, mostly caused by excessive neointima growth, sometimes even larger than the intimal hyperplasia observed with a simple balloon angioplasty.[2,3]

Mailing Address: Silméia Garcia Zanati Bazan •
Universidade Estadual Paulista Julio de Mesquita Filho Faculdade de Medicina Campus de Botucatu - Distrito Rubião Jr, s/n. Postal Code 18618-687, Botucatu, SP – Brazil
E-mail: HYPERLINK "mailto:sgz.bazan@unesp.br" sgz.bazan@unesp.br
Manuscript received January 07, 2019, revised manuscript September 20, 2019, accepted December 27, 2019

DOI: https://doi.org/10.36660/abc.20190650

More recently, drug-eluting stents (DES) were developed to reduce the high restenosis rate observed with BMS and the need for revascularization. Clinical trials have confirmed a reduction of 50-70% in the need for revascularizations of the target lesion with DES compared to BMS, although there has been no significant difference in overall mortality rate between them.[4-9] These results have led to the preferential recommendation of DES in coronary percutaneous intervention. However, these stents are expensive and require a long period of dual antiplatelet therapy to avoid thrombosis, and hence are not recommended for all patients.[10]

In some situations such as diabetes mellitus, small vessel involvement, in-stent stent, bifurcation lesions, long or multiple lesions, and saphenous vein graft, angioplasty with stent implantation present a high risk of restenosis (30-60%). In these conditions, DES are more consistently indicated.[11]

In addition to the above-mentioned situations, little is known about the importance of atherosclerotic plaques in carotid arteries and their correlation to in-stent restenosis. This correlation is possible since inflammation is common in both cases.[12] According to Corrado et al.,[13] in patients undergoing

coronary stent implantation, a higher frequency of in-stent restenosis is observed in those presenting greater carotid intima-media thickness (CIMT) and atherosclerotic plaques in carotid arteries.

As most risk indicators for in-stent restenosis concern coronary angiographic aspects, the objective of this study was to correlate, using ultrasonography, the carotid artery atherosclerotic profile with coronary in-stent restenosis, focusing on the presence of echolucent plaques.

Patients and methods

Patients

This study was approved by Botucatu Medical School Ethics Committee. All patients signed the informed consent form before participating in this study. We carried out a cross-sectional prospective study including 121 consecutive patients with chronic coronary artery disease, from February to December of 2015. All patients had undergone percutaneous coronary intervention and another angiography within 12 months. The angiographies were indicated for stable angina risk stratification, or after any confirmed myocardial ischemia in provocative tests (exercise stress test or cardiac scintigraphy with stress. Based on the directed interview we identified which patients had diabetes mellitus, dyslipidemia, or arterial hypertension. We also identified if they were tobacco users, and which medications they were taking. Coronary angiography detected previous stent implantation in coronary arteries (right coronary artery, circumflex coronary artery, anterior descending coronary artery, and their respective branches).

Carotid Artery Duplex Ultrasonography

All procedures were performed by an experienced sonographer using a Vivid S6 echocardiograph (General Electric Medical Systems, Tirat Carmel, Israel) equipped with an 8.0 MHz frequency linear array probe. Duplex ultrasonography of the carotid artery was performed with patient in supine decubitus position. Carotid images were analyzed according to the consensus statement from the American Society of Echocardiography carotid intima-media thickness task force[14] and the Mannheim Carotid Intima-Media Thickness Consensus,[15] and recorded on a compact disc. Classification of CIMT by age and gender were determined based on the 75th percentile of values proposed in the CAPS study.[16]

CIMT was measured using a double-line pattern visualized by echotomography on both common carotid arteries in a longitudinal image. This double-line pattern comprises the leading edges of the lumen–intima and media–adventitia interfaces. Mean values were calculated on a 10 mm segment next to the posterior wall of carotid bulb. Plaque was considered a focal structure when it encroached into the arterial lumen by at least 0.5 mm, or corresponded to 50% of surrounding CIMT value, or demonstrated a thickness of >1.5 mm, as measured from the media–adventitia to lumen–intima interface. Plaques were described according to the classification by Gray-Weale et al.[17] In brief, type I plaque is uniformly echolucent; type II is predominantly echolucent; type III is predominantly echogenic; and type IV is uniformly echogenic. For statistical analysis, types I and II were called echolucent and types III and IV echogenic.

Coronary angiography

Coronary angiographies were performed by transradial cardiac catheterization. After selective coronary angiography and stent identification, restenosis was evaluated by quantitative angiography. In-stent restenosis was defined as a lumen reduction of 50% or greater.[18,19]

Statistical analysis

Continuous variables were presented as medians and minimum and maximum values. Categorical variables were expressed as absolute values or frequency (%). The analysis of predictors of risk for in-stent restenosis at 12 months of follow-up was performed in two stages. In step 1, individual relative risk for each potential predictor was estimated. Then in phase 2, the model of multiple Cox regression was adjusted for the risk of in-stent restenosis with the predictors most strongly associated ($p < 0.05$) with restenosis detected in phase 1. Values of $p < 0.05$ were considered as statistically significant. All statistical analyses were performed using SPSS v21.0 software.

Results

The median age of the 121 patients was 60 years (1st quartile = 55, 3rd quartile = 68); 78 patients (64.5%) were male. Fifty-eight (47.9%) patients were smokers, 47 (38.8%) were diabetic, 91 (75.2%) had systemic hypertension, and 119 (98.3%) had dyslipidemia. After adjusting the Cox multiple-regression model for the risk of in-stent restenosis by potential predictors of restenosis, we observed that there was no statistically significant difference in distribution of these variables in the subgroups with or without in-stent restenosis (Table 1).

Stent locations were as follow: left anterior descending artery (LAD) in 50 patients (41.3%), right coronary artery (RCA) in 34 patients (28.1%), left circumflex artery (LCX) in 19 patients (15.7%), both LAD and RCA in 9 patients (7.4%), both LAD and LCX in 5 patients (4.1%), and both RCA and LCX in 4 patients (3.3%). Angiographies showed that 57 patients (47.1%) presented coronary in-stent restenosis, and the stent location did not influence in-stent restenosis rates (Table 1).

Most patients were taking aspirin (97.5%), statin (92.6%), angiotensin converting enzyme inhibitors or angiotensin receptor blockers (80.2%), beta-blockers (88.4%), and 27.3% were taking clopidogrel.

Fifty-five patients (45.5%) showed echolucent plaques in carotid arteries and 66 patients (54.5%) presented echogenic plaques or no plaques. Fifty patients (90.9%) with echolucent plaques and only seven (10.6%) of those with echogenic plaques or no plaques showed in-stent restenosis (Figure 1).

Ultrasonography images of carotid plaques and coronary angiographic findings are shown in Figures 2 and 3, respectively.

Table 1 – In-stent restenosis risk estimated for each variable

Variable	RR	95%CI	p
Age	0.99	0.96-1.02	0.555
Males	1.87	1.01-3.46	0.048
Medical history			
AH	0.85	0.47-1.51	0.567
DM	1.07	0.63-1.81	0.815
Tobacco use	1.21	0.72-2.03	0.478
Dyslipidemia	0.94	0.13-6.80	0.952
Carotid artery US			
Echolucent plaques	8.57	3.89-18.90	<0.001
CIMT (increased)	1.88	1.11-3.15	0.017
Coronary with stent			
LAD	1.23	0.72-2.07	0.450
RCA	0.76	0.44-1.32	0.330
LCX	0.85	0.45-1.60	0.607

AH: arterial hypertension; DM: diabetes mellitus; US: ultrasonography; CIMT: carotid intima-media thickness; LAD: left anterior descending artery; RCA: right coronary artery; LCX: left circumflex artery.

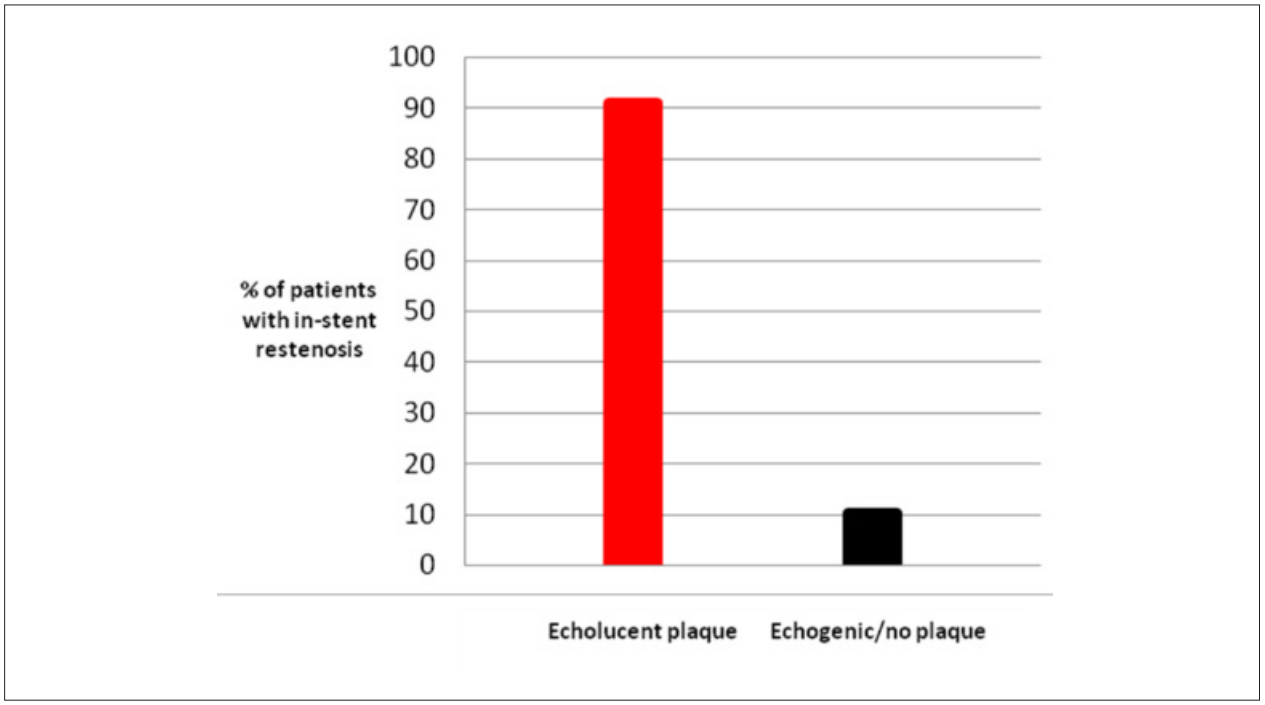


Figure 1 – *Percentage of patients with coronary in-stent restenosis in the subgroups of patients with echolucent plaques and patients with echogenic/no plaque in carotid arteries.*

The analysis of multiple regression revealed that the presence of echolucent plaques in carotid arteries increased the risk of coronary in-stent restenosis by 8.21 times (RR 8.21; 95%CI; 3.58-18.82; p<0.001). However, we observed that increased CIMT did not increase the risk of coronary in-stent restenosis (RR 1.03; 95%CI 0.60-1.76; p=0.897).

Discussion

This study revealed a clear correlation between echolucent atherosclerotic plaques in carotid arteries and coronary in-stent restenosis evaluated at 12 months after stent implantation. Patients with echolucent plaques in carotid arteries presented an 8.21 times greater risk of coronary in-stent restenosis than

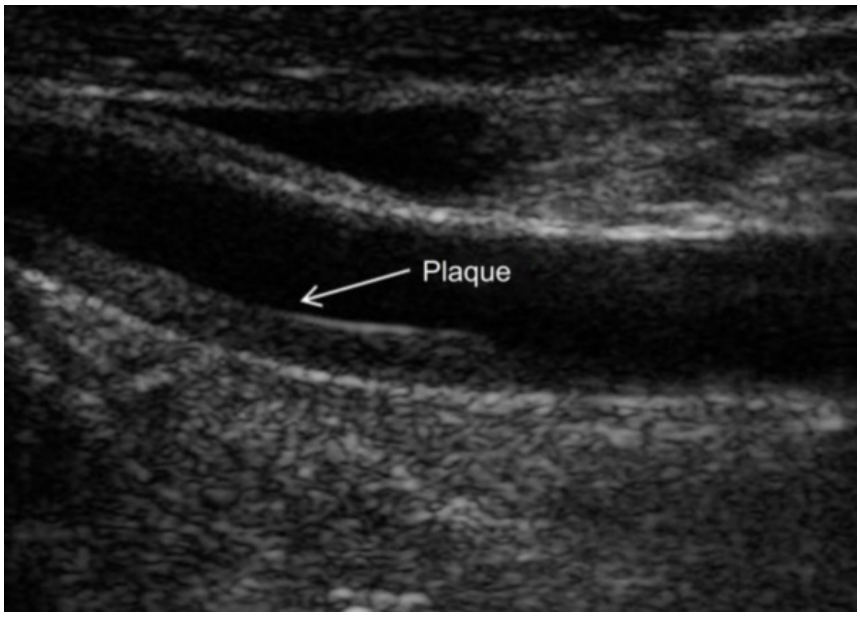


Figure 2 – *Ultrasound images of type II atherosclerotic plaque in the left carotid artery.*

those with echogenic plaques or no atherosclerotic plaques in carotid. A previous study, however, reported a correlation between echolucent plaques and coronary in-stent restenosis with an OR of 3.8.[20] Although often considered obsolete, BMS were used in both studies, which reflects most appropriately the current reality in Latin America. Though similar, the studies differ as to ethnicity and the second antiplatelet agent employed, as the 2008 study used ticlopidine. A possible justification for this correlation is an inflammatory state, which is common in both situations. Macrophages were the first inflammatory cells to be recognized to be associated with atherosclerosis.[21] Later, other types of inflammation-related leukocytes such as monocytes, neutrophils, and lymphocytes were detected in atherosclerotic plaques.[22,23] Cytokines are also related to acute and chronic inflammation, and their production depends on many strictly regulated factors during inflammation. A wide range of cytokines, such as TNF-α, IL-1, IL-2, IL-3, IL-6, CXCL8, IL-10, IL-12, IL-15, IL-18, IFN-γ, M-CSF, TGF-β1, TGF-β2, and TGF-β3 have been found in atherosclerotic plaques. Furthermore, under hyperlipidemic conditions TNF-α, IL-1, IL-6, IL-12, IL-15, and IL-18 are produced by macrophages.[24] Several studies have suggested the hypothesis that endothelial dysfunction — mostly caused by elevated LDL, tobacco, arterial hypertension, and diabetes mellitus — is the first step towards atherosclerosis. Therefore, each step of atherosclerosis would represent a different phase of the chronic inflammatory process.[25]

Platelets also play an important role in the atherogenic process. They can regulate immune and inflammatory responses by secreting inflammatory mediators that modulate leukocyte recruitment to the inflamed tissues. Activated platelets, which express P-selectin, have been detected in different phases of atherosclerosis.[26]

Echolucent atherosclerotic plaques — unlike echogenic plaques, which contain more calcium and fibrous tissue — are much richer in lipids, elastin, and inflammatory cells, with high macrophage concentration and metalloproteinase activity, which plays an important role in cellular differentiation, proliferation and migration, and also in vascular remodeling.[27] Echolucent plaque in carotid artery has been shown to be an independent predictor of stroke and acute coronary syndrome, including myocardial infarction.[28,29]

In-stent restenosis is caused by a combination of factors including endothelial denudation, mechanical trauma, and derangement of the tunica media and adventitia. An inflammatory reaction occurs in the stent structures, with leukocyte, monocyte, and macrophage infiltration; inflammation severity is directly proportional to arterial wall trauma. Mechanical injury of the vessel wall stimulates the migration of smooth muscle cells (from the tunica media) and myofibroblasts (from the tunica adventitia) to the tunica intima, where they proliferate.[30] Exposure of the vessel tunics facilitates contact with blood circulating factors, stimulating intima tunic hyperplasia. As time passes, cellularity decreases and the extracellular matrix begins to predominate in the restenosis lesion. Histopathological studies describe a more prolonged inflammatory reaction after stent implantation than after balloon angioplasty.[31]

Kornowski et al.[32] reported that inflammatory reaction of arterial wall in porcine coronary arteries was frequently observed 1 month after stent implantation. The inflammatory reaction was mainly composed of histiocytes, lymphocytes, and granuloma formation, and also neutrophils in the most severe inflammatory forms. There was a strong correlation between the extent of inflammatory reaction and the amount

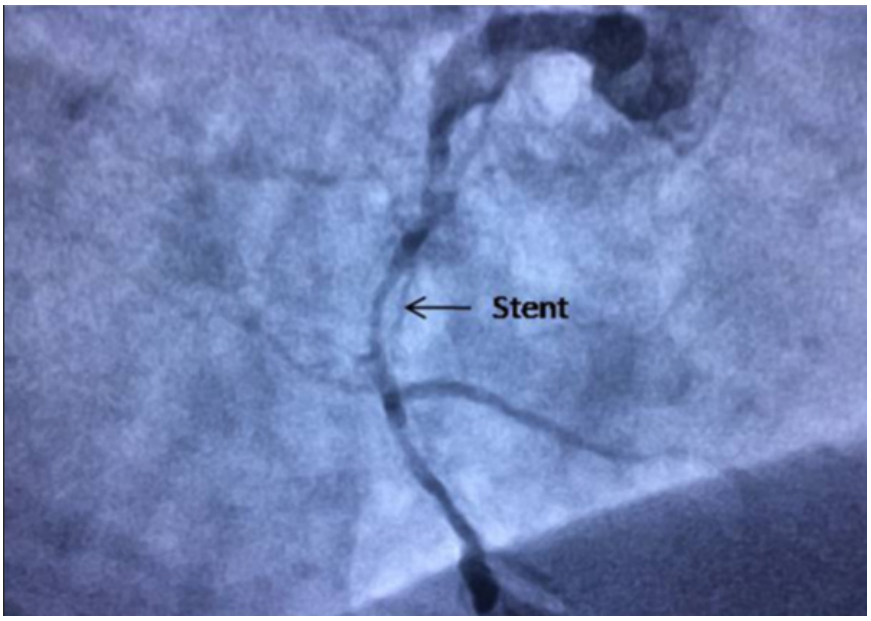


Figure 3 – *Coronary angiographic findings with stent restenosis in the right coronary artery.*

of neointimal formation within the stents. According to the above studies that evaluated the mechanisms of atherogenesis and in-stent restenosis, inflammation is an evident common link between echolucent plaque in carotid artery and coronary in-stent restenosis. Furthermore, Rothwell et al.[33] reported that plaque instability, i.e., with inflammation, is not a merely local vascular phenomenon, but occurs simultaneously at multiple sites in the systemic vascular bed.

Despite being a predictor of cardiovascular diseases, increased CIMT did not elevate the risk of in-stent restenosis. This is consistent with previous studies and with the concept that plaque size does not contribute as much as plaque instability to cardiovascular events.[20,34] This was possibly because carotid intima-media thickening is part of the arterial wall aging process, and not synonymous of subclinical atherosclerosis. However, cellular and molecular changes observed in intima-media thickening have been implicated in plaque development and progression.[14] Thus, an increase in CIMT with no concomitant plaques would have no relation to the inflammatory processes in atherosclerosis.

Study limitations

The external validity of this study is limited due to the evaluation of symptomatic patients diagnosed with stable angina only. However, the fact that all patients in this study underwent coronary angiography, which is the gold standard exam for the diagnosis of coronary stent restenosis, increases its internal validity. Another limitation found was that we did not study a group of patients submitted to DES.

Conclusion

The presence of echolucent atherosclerotic plaque in carotid artery represents a risk predictor of coronary in-stent restenosis and should be considered along with other risk predictors in the decision-making on the type of stent to be implanted in coronary angioplasty.

Author contributions

Conception and design of the research: Rodrigues CSA, Nunes HRC, Okoshi K, Hueb JC, Bazan SGZ; Data acquisition: Rodrigues CSA, Reis FM, Silveira CFSMP, Hueb LMS; Analysis and interpretation of the data and Writing of the manuscript: Rodrigues CSA, Bazan R, Reis FM, Silveira CFSMP, Hueb LMS, Carvalho FC, Nunes HRC, Okoshi K, Hueb JC, Bazan SGZ; Statistical analysis: Bazan R, Nunes HRC; Critical revision of the manuscript for intellectual content: Bazan SGZ.

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.

Sources of Funding

There was no external funding source for this study.

Study Association

This article is part of the thesis of master submitted by Cássia da Silva Antico Rodrigues from Universidade Estadual Paulista Julio de Mesquita Filho.

References

1. Hoffmann R, Mintz GS, Dussaillant GR, Popma JJ, Pichard AD, Satler LF, et al. Patterns and mechanisms of in-stent restenosis - A serial intravascular ultrasound study. Circulation. 1996; 94(6):1247-54.
2. Cutlip DE, Chauhan MS, Baim DS, Ho KK, Popma JJ, Carrozza JP, et al. Clinical restenosis after coronary stenting: perspectives from multicenter clinical trials. J Am Coll Cardiol, 2002;40(12):2082-9.
3. Karas SP, Gravanis MB, Santoian EC, Robinson KA, Anderberg KA, King SB. Coronary intimal proliferation after balloon injury and stenting in swine: an animal model of restenosis. J Am Coll Cardiol .1992;20(2):467-74.
4. Steele PM, Chesebro JH, Stanson AW, Holmes DR Jr, Dewanjee MK, Badimon L, et al. Balloon angioplasty. Natural history of the pathophysiological response to injury in a pig model. Circ Res. 1985;57(1):105-12.
5. Hill RA, Boland A, Dickson R, Dündar Y, Haycox A, McLeod C, et al. Drug-eluting stents: a systematic review and economic evaluation. Health Technol Assess. 2007;11(46):iii, xi-221.
6. Tu JV, Bowen J, Chiu M, Ko DT, Austin PC, He Y, et al. Effectiveness and safety of drug-eluting stents in Ontario. N Engl J Med. 2007;357(14):1393-402.
7. Abbott JD, Voss MR, Nakamura M, Cohen HA, Selzer F, Kip KE, et al. Unrestricted use of drug-eluting stents compared with bare-metal stents in routine clinical practice: findings from the National Heart, Lung, and Blood Institute Dynamic Registry. J Am Coll Cardiol. 2007;50(21):2029-36.
8. James SK, Stenestrand U, Lindbäck J, Carlsson J, Scherstén F, Nilsson T, et al. Long-term safety and efficacy of drug-eluting versus bare-metal stents in Sweden. N Engl J Med. 2009;360(19):1933-45.
9. King SB III, Smith SC Jr, Hirshfeld JW Jr, Jacobs AK, Morrison DA, Williams DO. ACC/AHA/SCAI. Guideline Update for Percutaneous Coronary Intervention. Circulation. 2008;117(2):261-95.
10. Hochholzer W, Trenk D, Frundi D, Blanke P, Fischer B, Andris K, et al. Time dependence of platelet inhibition after a 600-mg loading dose of clopidogrel in a large, unselected cohort of candidates for percutaneous coronary intervention. Circulation. 2005;111(20):2560–4.
11. Cutlip D, Abbott JD. Clinical use intracoronary bare metal stents. [Cited in 2020 dec 12] Available from: uotodate/com/contents/clinical-use-of-intracoronary-bare-metal-stents
12. Ross R. Atherosclerosis-an inflammatory disease. N Engl J Med. 1999;340(2):115-26.
13. Corrado E, Camarda P, Coppola G, Muratori I, Ciaramitaro G, Farinella M, et al. Prognostic role of endothelial dysfunction and carotid intima-media thickness in patients undergoing coronary stent implantation. Int Angiol. 2009;28(1):12-9.
14. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography carotid intima-media thickness task force. Endorsed by the society for vascular medicine. J Am Soc Echocardiogr.2008; 21(2):93–111.
15. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, et al. Mannheim Carotid Intima-Media Thickness Consensus. Cerebrovasc Dis. 2007; 23(1):75–80.
16. Lorenz MW, von Kegler S, Steinmetz H, Markus HS, Sitzer M. Carotid intima-media thickening indicates a higher vascular risk across a wide age range: prospective data from the Carotid Atherosclerosis Progression Study (CAPS). Stroke. 2006; 37(1):87-92.
17. Gray-Weale AC, Graham JC, Burnett JR, Lusby RJ. Carotid artery atheroma: comparison of preoperative B-mode ultrasound appearance with carotid endarterectomy specimen pathology. J Cardiovasc Surg. 1988; 29(6):676-81.
18. Beatt KJ, Serruys PW, Hugenholtz PG. Restenosis after coronary angioplasty: new standards for clinical studies. J Am Coll Cardiol. 1990;15(2):491-8.
19. Califf RM, Ohman EM, Frid DJ, Fortin DF, Mark DB, Hlatky MA, et al. Restenosis: the clinical issues. In: Topol EJ: Text book of interventional cardiology W.B. Saunders, Philadelphia: WB Saunders;1990.p.363-94.
20. Kitta Y, Obata JE, Takano H, Nakamura T, Kodama Y, Fujioka D, et al. Echolucent carotid plaques predict in-stent restenosis after bare metal stenting in native coronary arteries. Atherosclerosis 2008;197(1):177-82.
21. Gerrity RG, Naito HK, Richardson M, Schwartz CJ. Dietary induced atherogenesis in swine. Morphology of the intima in prelesion stages. Am J Pathol. 1979;95(3):775-92.
22. Hansson GK, Libby P. The immune response in atherosclerosis: a double-edged sword. Nat Rev Immunol. 2006; 6(7):508-19.
23. Galkina E, Ley K. Leukocyte influx in atherosclerosis. Curr Drug Targets 2007; 8(12):1239-48.
24. Tedgui A, Mallat Z. Cytokines in atherosclerosis: pathogenic and regulatory pathways. Physiol Rev 2006; 86(2):515-81.
25. Ross R, Glomset JA. Atherosclerosis and the arterial smooth muscle cell: proliferation of smooth muscle is a key event in the genesis of the lesions of atherosclerosis. Science. 1973;180(4093):1332-9.
26. Von Hundelshausen P, Weber C. Platelets as immune cells: bridging inflammation and cardiovascular disease. Circ Res 2007;100(1):27-40.
27. Gronholdt ML, Nordestgaard BG, Bentzon J, Wiebe BM, Zhou J, Falk E, et al. Macrophages are associated with lipid-rich carotid artery plaques, echolucency on B-mode imaging, and elevated plasma lipid levels. J Vasc Surg 2002;35(1):137-45.
28. Polak JF, Shemanski L, O'Leary DH, Lefkowitz D, Price TR, Savage PJ, et al. Hypoechoic plaque at US of the carotid artery: an independent risk factor for incident stroke in adults aged 65 years or older. Cardiovascular Health Study. Radiology. 1998; 208(3):649-54.
29. Honda O, Sugiyama S, Kugiyama K, Fukushima H, Nakamura S, Koide S, et al. Echolucent carotid plaques predict future coronary events in patients with coronary artery disease. J Am Coll Cardiol. 2004;43(7):1177-84.
30. Komatsu R, Ueda M, Naruko T, Kojima A, Becker AE. Neointimal tissue response at sites of coronary stenting in humans: macroscopic, histological, and immunohistochemical analyses. Circulation. 1998; 98(3):224-33.
31. Kleinman ME, Cipolla GD, Cui J, Chronos N, King SBI, Robinson KA. Stent implantation induces late arterial wall cellular proliferation compared to angioplasty in normal rabbits. J Am Coll Cardiol. 1997;29:312A.
32. Kornowski R, Hong MK, Tio FO, Bramwell O, Wu H, Leon MB. In-stent restenosis: contributions of inflammatory responses and arterial injury to neointimal hyperplasia. J Am Coll Cardiol. 1998;31(1):224-30.
33. Rothwell PM, Villagra R, Gibson R, Donders RC, Warlow CP. Evidence of a chronic systemic cause of instability of atherosclerotic plaques. Lancet. 2000;355(9197):19-24.
34. Libby P, Aikawa M. Stabilization of atherosclerotic plaques: new mechanisms and clinical targets. Nat Med. 2002;8(11):1257-62.

Carotid Artery Atherosclerotic Profile as a Progression Marker for Cardiovascular Disease

Guilherme Brasileiro de Aguiar[1] *and José Guilherme Mendes Pereira Caldas*[2]

Faculdade de Ciências Médicas da Santa Casa de São Paulo,[1] *São Paulo, SP - Brasil*

Instituto de Radiologia do Hospital das Clínicas (InRad) - Faculdade de Medicina, Universidade de São Paulo,[2] *São Paulo, SP - Brazil*

Short editorial related to the article: Carotid Artery Atherosclerotic Profile as Risk Predictor for Restenosis After Coronary Stenting

Conditions directly linked to atherosclerosis are among the main causes of mortality worldwide, notably ischemic stroke and coronary artery disease (CAD).[1] Diagnosing cardiovascular disease or its progression in the early stages, aiming to apply measures that can prevent or delay its progression and subsequent complications is currently a major challenge.[2] The identification and characterization of atherosclerotic plaques allows the identification of a significant number of patients with low or intermediate risk scores.[2] Many of these patients would not be identified by the available algorithms for cardiovascular diseases, which could result in the lack of correct management.

The quantification of the carotid artery plaque may be a measure of atherosclerosis, which should be associated with future risk of atherosclerotic cardiovascular disease, encompassing coronary, cerebrovascular, and peripheral arterial diseases.[3] It is already known that impaired endothelial function and increased carotid intima-media thickness are substantial events in the atherosclerotic process,[4,5] with imaging of carotid features being used to predict the risk of cardiovascular events.[3]

Atherosclerosis is a diffuse inflammatory process that affects the arterial intima with extensive lipid deposition, foam cell formation, and vascular smooth muscle cell migration.[6] The resulting plaque can cause symptoms due to progressive vessel narrowing or small fragment migration.

The diagnosis of carotid atherosclerotic plaque has shifted from pure stenosis quantification to plaque characterization, which allows an improved pathophysiological understanding, and for more precise patient risk stratification and management.[3] Measurement of the intima-media thickness (IMT) and the plaque score (PS) – both using carotid ultrasonography - provide information on the extent of structural vascular damage[5] reflecting a possible coronary heart involvement.

Thus, using ultrasound for the detection and evaluation of atherosclerosis, particularly through carotid plaque assessment, and more recently, femoral plaque assessment, is becoming increasingly utilized in clinical decision-making for both at-risk and prevalent CAD patients.[7] Nevertheless, limited outcome-based research has confirmed the association between ultrasound-assessed carotid plaque burden and cardiovascular events.[7]

Representing a systemic impairment, the study of carotid plaques provides indirect information about the atherosclerotic profile and also about the greater or lesser risk associated with CAD.[6]

In the article "Carotid artery atherosclerotic profile as risk predictor for restenosis after coronary stenting" the authors go beyond the usual use of carotid images for cardiovascular risk tracking.[8] By evaluating more than 100 patients undergoing percutaneous coronary intervention, they correlate the presence of echolucent atherosclerotic plaques in the carotid artery with an increased risk of coronary in-stent restenosis. This finding may introduce a new tool in the follow-up of CAD patients and, maybe, influence the decision regarding the type of stent to be implanted in coronary angioplasty.

Keywords

Cardiovascular Diseases; Atherosclerosis; Mortality; Coronary Artery Disease; Stroke; Plaque, Atherosclerosis.

Mailing Address: José Guilherme Mendes Pereira Caldas •
Universidade de São Paulo – Neuroradiologia - Rua Dr. Alceu de Campos Rodrigues, 309 sl 21. Postal Code 04544-000, São Paulo, SP – Brazil
E-mail: jgmpcaldas@uol.com.br

DOI: https://doi.org/10.36660/abc.20210229

References

1. Corrado E, Camarda P, Coppola G, Muratori I, Ciaramitaro G, Farinella M, et al. Prognostic role of endothelial dysfunction and carotid intima-media thickness in patients undergoing coronary stent implantation. Int Angiol 2009; 28(1):12-9.
2. Zhu G, Hom J, Li Y, Jiang B, Rodriguez F, Fleischmann D, et al. Carotid plaque imaging and the risk of atherosclerotic cardiovascular disease. Cardiovasc Diagn Ther 2020; 10(4):1048-67.
3. Ojima S, Kubozono T, Kawasoe S, Kawabata T, Miyata M, Miyahara H, et al. Association of risk factors for atherosclerosis, including high-sensitivity C-reactive protein, with carotid intima-media thickness, plaque score, and pulse wave velocity in a male population. Hypertens Res 2020; 43(5):422-30.
4. Grubic N, Colledanchise KN, Liblik K, Johri AM. The Role of Carotid and Femoral Plaque Burden in the Diagnosis of Coronary Artery Disease. Curr Cardiol Rep 2020; 22(10):121.
5. Moreyra E Jr, Moreyra C, Tibaldi MA, Crespo F, Arias V, Lepori AJ, et al Concordance and prevalence of subclinical atherosclerosis in different vascular territories. Vascular 2020; 28(3):285-94.
6. Negrão EM, Freitas MCDNB, Marinho PBC, Hora TF, Montanaro VVA, Martins BJAF, et al. Coronary Calcium Score and Stratification of Coronary Artery Disease Risk in Patients with Atherosclerotic and Non-Atherosclerotic Ischemic Stroke. Arq Bras Cardiol 2020; 115(6):1144-51.
7. Daghem M, Bing R, Fayad ZA, Dweck MR. Noninvasive Imaging to Assess Atherosclerotic Plaque Composition and Disease Activity: Coronary and Carotid Applications. JACC Cardiovasc Imaging 2020; 13(4):1055-68.
8. Rodrigues CSA, Bazan R, Reis FM, Silveira CFSMP, Hueb LMS, Carvalho FC,et al. Perfil Aterosclerótico da Artéria Carótida como Preditor de Risco para Reestenose após Implante de Stent Coronário. Arq Bras Cardiol. 2021; 116(4):727-733.

Statins Prescriptions and Lipid Levels in a Tertiary Public Hospital

André Schmidt,[1] Henrique Turin Moreira,[1] Gustavo Jardim Volpe,[1] Vamberto B. Foschini,[1] Thiago Florentino Lascala,[1] Minna Moreira Dias Romano,[1] Marcus Vinícius Simões,[1] José Ernesto dos Santos,[1] Benedito Carlos Maciel,[1] José Antonio Marin-Neto[1]

Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (HCFMRP-USP),[1] Ribeirão Preto, SP – Brazil

Abstract

Background: **The development of a new class of medications that are highly capable of reducing LDL-cholesterol renewed the interest in the characterization of familial hypercholesterolemia patients. Nevertheless, little is known about the lipid profile of patients in tertiary healthcare centers in Brazil in order to better estimate the real occurrence of familial hypercholesterolemia, with initial suspect of LDL-cholesterol levels above 190 mg/d/L.**

Objectives: **This study evaluated the lipid profile (total cholesterol and LDL-cholesterol) in ambulatory patients from a general tertiary public hospital.**

Methods: **Retrospective study comparing prescriptions of statins and lipid profile results. The significance level was established in 5%.**

Results: **In one year, 9,594 individuals received statin prescriptions, of whom 51.5% were females and the mean age was 63.7±12.9 years-old (18 to 100 years-old). Thirty-two medical specialties prescribed statins. Cardiology was responsible for 43% of the total. Nearly 15% of those patients with a prescription did not have a recent total cholesterol result and 1,746 (18%) did not have a recent LDL-cholesterol measurement. The occurrence of the latter between 130 and 190 mg/dL was present in 1,643 (17.1%) individuals, and 228 (2.4%) patients had an LDL-cholesterol ≥190mg/dL among those using statins at distinct doses. Only two statins were used: simvastatin and atorvastatin. The first was prescribed in 77.6% of the prescriptions.**

Conclusion: **In this cross-sectional cohort at a tertiary general hospital, statins have been widely prescribed but with little success in achieving recognized levels of control. There is probably a significant number of FH individuals in this cohort that need to be properly diagnosed in order to receive adequate treatment due to its prognostic implications. (Arq Bras Cardiol. 2021; 116(4):736-741)**

Keywords: **Hydroxymethylglutaryl CO-Reductase Inhibitors; Dyipidemias; Hyperpoprotein Type II. Hypercholesterolemia Familial/therapy; Cholesterol; Public Hospital; Lipid Profile.**

Introduction

Although a recent metanalysis indicates an incidence of 1:250 for familial hypercholesterolemia (FH) in the general population,[1] the real specific prevalence of cases with high cholesterol values in tertiary public healthcare outpatient centers in Brazil is unknown. In general, these centers concentrate patients with more comorbidities and severe clinical presentations.

Only few studies have evaluated the cost-effectiveness of statins use in the Brazilian unified public health system (*Sistema Único de Saude* – SUS);[2,3] however, adherence to treatment was evaluated in selected samples (women) and reached only 15.5% in a small series.[4] The recent incorporation to the therapeutic arsenal of new highly effective medications for hypercholesterolemia control,[5,6] although with high financial costs, led to a convergence of patients with a very ominous lipid profile to the public health system looking for the prescription of these medications. Nevertheless, little is known about the lipid profile and treatment of these outpatients in tertiary centers.

Our purpose is to report the real profile of statins prescription in a tertiary public hospital, profile of resultant lipids, and possible presence of FH patients (LDL-cholesterol > 190 mg/dL) despite the use of statins.

Methods

This cross-sectional study was based on a systematic electronic data collection from the institution clinical records, including patients of both genders ≥ 18 years-old who received an ambulatory prescription of any statin, in the Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (HCFMRP-USP), which was a tertiary public teaching institution in 2016. In addition, total cholesterol (TC) and/or LDL-

Mailing Address: André Schmidt •
Universidade de São Paulo Faculdade de Medicina de Ribeirão Preto - Centro de Cardiologia - HCFMRP-USP Av. Bandeirantes, 3900. Postal Code 14048-900, Ribeirão Preto, SP – Brazil
E-mail: aschmidt@fmrp.usp.br
Manuscript received August 06, 2019, revised manuscript February 25, 2020, accepted March 16, 2020

DOI: https://doi.org/10.36660/abc.20190513

cholesterol (LDL-c) measurements were obtained later that year. For individuals with more than one measurement in such year, only the last one was considered. We collected information regarding gender, age, used statin and its dose, and the specialty that requested the prescription. Since an electronic search was performed in clinical records, no data were obtained about comorbidities and clinical and anthropometric parameters. This study was approved by the local institutional review board (CAAE 16516819.0.0000.5440).

Statistical analysis

A descriptive analysis was carried out, and values were expressed as mean and standard deviation if a normal distribution by the Kolmogorov-Smirnov test was observed. Qualitative variables were expressed as percentages, and the Pearson's correlation test was used to correlate TC and LDL-c values. Unpaired Student's *t*-test was applied to compare age categories.

SPSS v.25 (IBM Corporation, EUA) was the statistical package used, and the level of significance was established as 5%.

Results

Prescriptions

In 2016, 9,594 patients followed at our institution received an ambulatory prescription of statins. A discrete larger number of women (51.5% - 4,942 patients) received a prescription of statins. Mean age was 63.7±12.9 years-old (18 to 100 years-old). A TC of 8,110 (84.8%) and LDL-c level of 7,848 (82.0%) were available, indicating that 1,484 (15.2%) patients received a prescription without a recent TC measurement, whereas 1,746 (18.0%) did not present an LDL-c measurement. All medical specialties had patients prescribed without a recent lipid profile, but nearly 75% of them had a statin prescribed without a LDL-c recent result in Vascular Surgery.

Among the 32 medical specialties that prescribed statins, Cardiology was responsible for 43.5%, followed by Vascular Surgery (9.2%) and Nephrology (8.6%). The remaining 32% was distributed among the other medical specialties of this public tertiary hospital, and Nutrology was responsible for only 106 (1.1%), as seen in Table 1.

Lipid profile

The mean TC of four samples was 174.4± 49.5 mg/dL (40.0–739.0 mg/dL) and mean LDL-c was 101.1±40.0 mg/dL (4.0–635.0 mg/dL). A strong correlation between these two variables was observed (r= 0.94 - p<0.001). Figure 1 presents the individual values for TC and LDL-c.

Women had significantly worse values for TC (183.3±49.9 *versus* 164.5±47.0 mg/dL; p<0.001) and LDL-c (107.1±40.9 *versus* 94.3±7.9 mg/dL; p<0.001) than men, although the mean age was equal: 63.65±13.56 *versus* 63.36±12.60; p=0.29.

LDL-c levels above 130 mg/dL and below 190 mg/dL were observed in 1,643 (17.1%) patients with a prescription of statins. In addition, 18.2% of the total sample did not have an LDL-c measurement despite the prescription of a statin. Therefore, a considerable number of patients presented an LDL-c value above recommendations of guidelines, despite using statins and without taking other comorbidities into account.

Table 1 – Prescription of statins according to medical specialty in the year of 2016

Specialty	Number (%)
Cardiology	4160 (43.5)
Vascular surgery	1576 (9.2)
Nephrology	819 (8.6)
Neurology	731 (7.6)
Geriatrics	657 (6.9)
Endocrinology	653 (6.8)
Nutrology	94 (1.0)
Other 25 specialties	1,576 (16.5)
Total	9,567 (100)

Finally, 228 (2.4%) patients presented LDL-c ≥ 190 mg/dL and were prescribed distinct statins in various dosages. Two-thirds (152) were females and had a mean age below the whole sample (55±15 *versus* 63±13years-old; p<0.05), which is a possible indicator of the occurrence of FH in this tertiary hospital group of patients.

Statin use

Since this is a hospital part of the Brazilian public health system, only two statins were available for prescription: Simvastatin e Atorvastatin. The first was 77.6% (7,474) of the recipes. Simvastatin 40 mg was the most used dosage in 3,760 (39.3%) prescriptions, followed by its dosage of 20 mg in 3,158 (33.0%). Atorvastatin 40 mg was the third most used in 1,087 (11.4%) ambulatory prescriptions. Table 2 summarizes TC and LDL-c levels according to the type of statin and dosage in the prescription.

We verified that higher simvastatin dosages were probably delivered in patients with the worst lipid profile, indicating that dosage adjustments were being applied. Both TC and LDL-c levels reduced without statistical significance (p>0.05) for atorvastatin until a daily dosage of 40 mg was achieved. The 80-mg dosage was prescribed to only 3% of our sample. Those, individuals had a worse response, since both TC and LDL-c levels were higher than in those who received atorvastatin 40 mg daily (p<0.05). In general, higher dosages were prescribed that suggest a better lipid level control.

Mean TC and LDL-c levels were significantly (p<0.05) lower in patients prescribed by Cardiology in comparison to other specialties, which is the only specialty with a mean TC below 170 mg/dL and mean LDL-c below 95 mg/dL (Table 3).

Discussion

In this study we verified that prescribing statins is common practice in a tertiary public hospital environment, probably

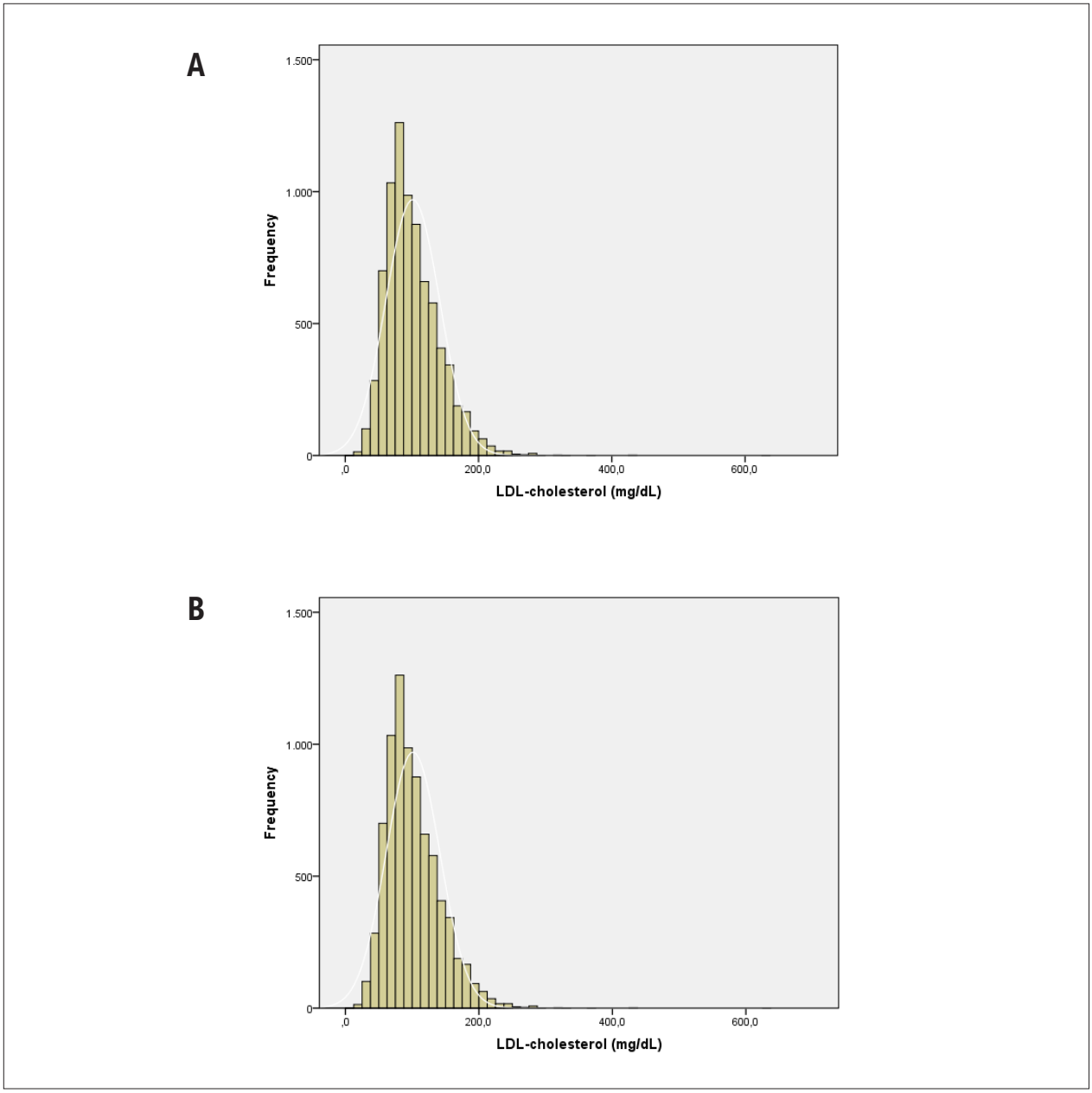


Figure 1 - *Histograms of the absolute values of total cholesterol (A) and low-density cholesterol fraction – LDL-c; (B) in the sample of patients from Hospital das Clínicas, Faculdade de Medicina de Ribeirão Preto, year 2016*

related to the elevated presence number of cardiovascular comorbidities present in this selected sample. Vannucchi et al., in our institution in the late 1970s, described the lipid profile of nearly 1,700 patients obtained during a three-year period. They verified that 25.5% of the exams presented at least one diagnosis of dyslipidemia. Yet, due to the absence of specific treatments back then, nothing was discussed about this topic.[7] In the literature, Pant et al. reported the lipid profile of a tertiary hospital in Nepal.[8] This study obtained a convenience outpatient sample of patients that did not use statins or had comorbidities and verified that in 408 patients with a mean age of 50, LDL-c and TC were 113±41 mg/dL and 180±54 mg/dL, respectively. Another study from Turkey used the lipid profile results to identify FH patients and concluded that many patients with elevated LDL-c were not receiving any specific treatment.[9]

As an original contribution of our investigation, we reported that prescription of statins is disseminated at our institution. This indicates a widespread of this cardiovascular risk factor, apparently without a specific target, since the great variability of the mean values for each specialty is notably those dealing directly with cardiovascular diseases (vascular surgery division in the Surgery Department and the Neurology Department).

Table 2 – Mean serum levels of total cholesterol and its low-density cholesterol fraction according to statin used and its daily dosage. Patients using intermediary dosages were excluded

Statin and daily dosage	Number of patients	Total cholesterol (mg/dL) mean±SD	LDL-c (mg/dL) mean±SD
Simvastatin			
10 mg	302	168±43	96±36
20 mg	3164	177±49	103±40
40 mg	3764	173±52	100±41
80 mg	57	193±66	110±34
Atorvastatin			
10 mg	92	184±63	109±53
20 mg	481	176±56	100±42
40 mg	1088	170±52	97±41
80 mg	283	182±51	109±43

SD: standard deviation.

The fact that the Nutrology Division, responsible for 1.1% of the prescriptions, presented the highest lipid levels probably indicates that resistant patients or those with FH are probably referred to their tertiary level outpatient clinic. In addition, this specific sample suggests that new medications, such as ezetimibe, which reduce the intestinal absorption of cholesterol and the proprotein convertase subtilisin/kexin type 9 (*PCSK9*), although not available for prescription in the public health system, may be needed.

Atorvastatin prescription was modest (22%), considering that an elaborated procedure for statin prescription with the inclusion of laboratorial results and underutilization of this statin may have occurred. The elevated percentage of patients receiving statins without at least one annual lipid measurement suggests that local clinical protocols or societies guidelines were not observed.[10] Additionally, in a great number of patients, no dosage adjustments were performed, and the prescription dosage was automatically repeated.

Periodical dosage adjustments guided by well-established institutional clinical protocols should have been applied. Patients from services that are highly associated with the occurrence of cardiovascular diseases without well-established treatment protocols presented higher mean lipid levels than those observed in Cardiology ambulatories where they exist, suggesting that the enforcement of risk factors control is distinct despite being in the same nosological context.

Although the mean lipid levels of our sample were within those acceptable for a general population, the large number of individuals with elevated cardiovascular risk in our sample suggests the existence of space for improvement. In addition, there is a significant proportion of patients with very high lipid levels despite the use of statins. It may indicate an adherence to treatment problem. Since these statins are distributed without charge by the public health system, there is no point in considering financial restrictions and, for the study period, no lack of medication in the public pharmacies was reported.

Another relevant aspect to be considered is that female patients had higher lipid levels compared to male patients. The proportion of women older than 60 years-old was reported in other studies[11,12] without any clear reason. The role of menopause in these increased values needs to be considered. Although speculative in this context, it is plausible to attribute some lenience with dosage adjustments in this gender for controlling coronary artery disease risk factors, as previously reported.[13]

The preponderant prescription of simvastatin is probably related to its widespread availability in the ambulatory public health system. Atorvastatin needs a special request since it is included in a program to deliver high-cost medications of the São Paulo state government and preferred in refractory patients or in simvastatin intolerance. In general, we observed a high dosage use of both statins.

The high variability in lipid levels related to the various dosages indicates that adjustments and use of a more effective statin is a necessity, reinforcing the need for well-established institutional clinical protocols to improve drug and dosage selection.

Finally, the number of individuals with LDL-c above 190 mg/dL, despite the use of statins, is significantly higher than the one reported in the general population. This percentage (2.4%) certainly reflects the high concentration of patients, in this tertiary level, with more comorbidities. Nevertheless, since these patients were younger, the occurrence of FH is a strong possibility that needs systematic investigation after reaching the higher statins dosages.

Limitations

Our study presents many limitations. First, we did not include the complete lipid profile, with triglycerides and high-density cholesterol (HDL-c) levels, because our focus was on the use of statins, and their levels do not interfere with statin prescription. No data on the use of ezetimibe were collected, even though its use may have contributed

Table 3 – Mean serum levels of total cholesterol and its low-density cholesterol fraction (LDL-c) according to medical specialty in the year 2016

Specialty	Total cholesterol (mg/dL)	LDL-c (mg/dL)
Cardiology	166.1±45.1	94.6±36.3
Vascular surgery	179.5±49.3	103.8±40.3
Nephrology	171.6±45.0	98.4±37.2
Neurology	183.3±58.5	104.6±46.6
Geriatrics	171.9±45.1	104.5±36.9
Endocrinology	175.0±51.8	104.2±39.4
Nutrology	186.5±47.0	112.7±41.1
Others	192.5±53.4	115.3±44.6

to the reduction of lipids,[14] because it was not included in the list of medications available in the Brazilian public health system, although some patients may have acquired it by suggestion of their physicians. Another limitation is the fact that comorbidities and anthropometric data were not obtained. Unfortunately, in studies like this, with a large number of patients, revision of patient's notes individually is not feasible and as the big data system is being established at the moment of the data collection of our study, many errors could have occurred. For this reason, there is no cardiovascular risk numbers.

Conclusions

In this cross-sectional cohort of a tertiary hospital, we observed that prescription of statins is widespread, but clear TC and LDL-c targets are not achieved in a high proportion of patients. It is possible that a high percentage of FH exists and should be better investigated, for prognostic reasons. Institutional adherence to uniform clinical diagnostic and treatment protocols would probably increase a better control of dyslipidemia in this tertiary institution. It would also allow resource allocation for prescription of new effective medications, such as PCSK9 inhibitors in selected patients as recommended by guidelines.[15]

Author contributions

Conception and design of the research: Schmidt A, Maciel BC; Data acquisition: Moreira HT, Volpe GJ, Foschini VB, Lascala TF; Analysis and interpretation of the data: Schmidt A, Volpe GJ; Statistical analysis: Schmidt A, Moreira HT, Volpe GJ, Foschini VB; Writing of the manuscript: Schmidt A, Maciel BC, Marin-Neto JA; Critical revision of the manuscript for intellectual content: Moreira HT, Volpe GJ, Foschini VB, Romano MMD, Simões MV, Santos JE, Maciel BC, Marin-Neto JA.

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.

Sources of Funding

There was no external funding source for this study.

Study Association

This study is not associated with any thesis or dissertation.

References

1. Akioyamen LE, Genest J, Shan SD, Reel RL, Albaum JM, Chu A, et al. Estimating the prevalence of heterozygous familial hypercholesterolaemia: a systematic review and meta-analysis. BMJ Open. 2017;7(9):e016461.
2. Ribeiro RA, Duncan BB, Ziegelmann PK, Stella SF, Vieira JLC, Restelatto LMF, et al. Cost-effectiveness of high, moderate and low-dose statins in the prevention of vascular events in the Brazilian public health system. Arq Bras Cardiol. 2015;104(1):32-44.
3. Araujo DV, Souza CPR, Bahia LR, Rey HCV, Santos Jr B, Tura BR, et al. Analysis of cost-effectiveness of simvastatin versus atorvastatin in the secondary prevention of cardiovascular events within the Brazilian public healthcare system. Value Health. 2011;14(5 Suppl 1):S29-32.
4. Bonfim MR, Hansen A, Turi BC, Zanini GS, Oliveira ASB, Amaral SL, et al. Adherence to statin treatment and associated factors in female users from the Unified Health System (SUS). Rev Esc Enferm USP. 2014;48(3):477-83.
5. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl JMed. 2017;376(18):1713-22.
6. Schwartz GG, Steg PG, Szarek M, Bhatt DL, Bittner VA, Diaz R, et al. Alirocumab and cardiovascular outcomes after acute coronary syndrome. N Engl J Med. 2018;379(22):2097-2107.
7. Vannucchi H, dos Santos JE, Marchini JS et al. Lipidograms in patients at the Clinical Hospital of the Ribeirao Preto Medical School. AMB Rev Assoc Med Bras. 1981;27(9):261-3.
8. Pant P, Hamal PK, Gurung D, Upreti K, Subedi K. Lipid profile in a tertiary care center. JNMA J Nepal Med Assoc. 2010;49(178):147-50.
9. Haymana C, Berlik H, Gunes Y et al. Identifying undiagnosed or undertreated patients with familial hypercholesterolemia from the laboratory records of a tertiary medical center. Turk Kardiyol Dern Ars. 2017;45(8):731-8.

10. Faludi AA, Izar MCO, Saraiva JFK, Chacra APM, Bianco HT, Afiune Neto A, et al.,Sociedade Brasileira de Cardiologia. Atualização da Diretriz Brasileira de Dislipidemias e Prevenção da Aterosclerose – 2017. Arq Bras Cardiol. 2017;109(2 Supl 1):1-76.

11. Range JT, LaFontaine PR, Ryder PT, Polston M. Factors associated with adherence to statin medications of patients enrolled in a self-insured university health plan. Clin Ther. 2018;40(10):1692-1700.

12. Carroll MD, Fryar CD, Nguyen DT. Total and high-density lipoprotein cholesterol in adults: United States, 2015-2016. NCHS Data Brief. 2017 Oct;(290):1-8.

13. Gottlieb S, Harpaz D, Shotan A, Boyko V, Leor J, Cohen M, et al. Sex differences in management and outcome after acute myocardial infarction in the 1990s: A prospective observational community-based study. Israeli Thrombolytic Survey Group. Circulation. 2000;102(20):2484-90.

14. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Eng J Med. 2015;372(25):2387-97.

15. Santos RD, Gagliardi AC, Xavier HT, Casella Filho A, Araújo DB, Cesena FY, et al. First Brazilian Guidelines for Familial Hypercholesterolemia. Arq Bras Cardiol. 2012;99(2 Suppl 2):1-28.

Statin Use and Hypercholesterolemia: Are the Current Guidelines' Recommendations Being Followed?

Renato Jorge Alves[1,2]

Departamento de Cardiologia na Santa Casa de Misericórdia de São Paulo,[1] *São Paulo, SP - Brazil*
Faculdade de Ciências Médicas, Santa Casa de São Paulo,[2] *São Paulo, SP - Brazil*
Short Editorial related to the article: Statins Prescriptions and Lipid Levels in a Tertiary Public Hospital

Despite advances in treating cardiovascular diseases, acute myocardial infarction and stroke are still the main causes of death worldwide.[1]

The prevention of coronary atherosclerotic disease (CAD), represented by the treatment of low-density lipoprotein cholesterol (LDL-c), is one of the main alternatives for increasing the survival of patients with cardiovascular risk factors. Case-control, observational, and genetic studies confirm the importance of increased cholesterol level as one of the main modifiable risk factors for cardiovascular disease, especially for CAD and ischemic stroke. The reduction in LDL-c throughout life has been associated with a lower risk of developing CAD. There seems to be a causal relationship between LDL-c and CAD, which is continuous and which depends on the magnitude of the reduction in LDL-c.[2-5]

After the Japanese biochemist Akira Endo discovered statins in 1976, intervention studies with this drug class changed the CAD prevention concern. Currently, statins (3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors) are recommended by all guidelines as first-line drugs in the pharmacological treatment of hypercholesterolemia for primary and secondary prevention of CAD. This drug class acts by inhibiting cholesterol synthesis, thus increasing expression of receptors, resulting in greater removal of plasmatic LDL.[6-8]

The most robust meta-analysis on statins evaluated data from 170,000 patients in 26 clinical studies. This publication highlighted the comparison of statins versus placebo and more versus less potent statins. It was observed that, for LDL-c reduction of 1 mmol/L or 40 mg/dL, there was an average reduction of 22% in the main cardiovascular outcomes. The analysis also showed that the greater the reduction in LDL-c, the greater the benefit achieved from the treatment. Large clinical trials with statins have demonstrated that the greater the absolute reduction in LDL-c, the greater the reduction in the relative risk of cardiovascular events.[5] To date, no threshold has been identified below which lipid-lowering treatment would fail to promote cardiovascular benefit; however, very low LDL-c levels were evaluated for a short period of time.[9-11]

In the article "Statins Prescriptions and Lipid Levels in a Tertiary Public Hospital"[12] the statin prescription is frequent, possibly due to the recognition of dyslipidemia as a relevant cardiovascular risk factor. However, it was performed without a specific LDL-c target, without dose adjustment, and without at least one annual control test, showing that the guidelines' recommendations are not fully considered. Moreover, it showed that the prescription without evaluation of blood cholesterol occurred predominantly in Vascular Surgery and that Cardiology was the specialty with the highest number of statin prescriptions. Despite this, a considerable percentage of individuals have LDL-c above that recommended in primary prevention guidelines. On the order hand, it is interesting to note that compared with the AHA/ACC guideline, the Brazilian guideline seems to classify a larger proportion of primary prevention patients into higher-risk categories, increasing the statin eligibility criteria.[13] It was also noted that the use of statins by the Public Health System is cost-effective and that, among the treated individuals, 2.4% had LDL-c $\geq$ 190 mg/dL. This LDL-c level, higher than that registered in the general population, accompanied by a mean age lower than the total sample (55 $\pm$ 15 versus 63 $\pm$ 13 years, $p < 0.05$), suggests the possibility of the presence of familial hypercholesterolemia in that group. Thus, a more cautious follow-up would be recommended, as there would be a greater cardiovascular risk in this population.[14,15]

The two statins used in this survey, simvastatin (78%) and atorvastatin (22%), showed that plasma cholesterol and LDL-c concentrations were lower in patients receiving prescriptions from cardiology. Therefore, it would be expected that the achievement of goals recommended in the guidelines, not achieved in a large percentage of patients, should have been more achieved by this specialty.

The results found in this study illustrate the need not only for more accurate laboratory diagnosis, but mainly for more effective lipid-lowering treatment. We have sufficient data on the safety and efficacy of statins, including in acute coronary syndrome.[16]

More aggressive lipid-lowering therapy and early diagnosis should be emphasized. Statins continue to be the gold standard in the pharmacological treatment of hypercholesterolemia. However, in addition to enhancing the dosage, new drugs with proven scientific evidence in this therapeutic arsenal, such as ezetimibe and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, have already been shown to reduce cardiovascular risk safely.

Keywords

Cardiovascular Diseases; Stroke; Myocardial Infarction; Mortality; Atherosclerosis; Risk Factors; Hydroxymethylglutaryl –CoA Reductase Inhibitors; Hospitalization; Hospitals, Public.

Mailing Address: Renato Jorge Alves •
Irmandade da Santa Casa de Misericórdia de São Paulo - Departamento de Medicina - Rua Cesário Motta Jr., 112. Postal Code 04126-000, São Paulo, SP – Brazil
E-mail: renatoalves178@gmail.com

DOI: https://doi.org/10.36660/abc.20210089

References

1. Smith SC Jr, Collins A, Ferrari R, Holmes DR Jr, Logstrup S, McGhie DV, Ralston J, Sacco RL, Stam H, Taubert K, Wood DA, Zoghbi WA; World Heart Federation; American Heart Association; American College of Cardiology Foundation; European Heart Network; European Society of Cardiology. Our time: a call to save preventable death from cardiovascular disease (heart disease and stroke). J Am Coll Cardiol. 2012;60(22):2343-8.

2. Management of the long-term intervention with pravastatin in ischaemic disease (LIPID) study after the scandinavian simvastatin survival study (4S) Andrew M. Tonkin AM. Am J Cardiol. 1995; 28;76(9):107C-112C.

3. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet. 2004;364(9438):937-52.

4. Ference BA, Yoo W, Alesh I, Mahajan N, Mirowska KK, Mewada A, et al. Effect of long-term exposure to lower low-density lipoprotein cholesterol beginning early in life on the risk of coronary heart disease: a Mendelian randomization analysis. J Am Coll Cardiol. 2012;60(25):2631-9.

5. Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhala N, et al; Cholesterol Treatment Trialists' (CTT) Collaboration. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials. Lancet. 2010;376(9753):1670-81.

6. Faludi AA, Izar MCO, Saraiva JFK, Chacra APM, Bianco HT, Afiune AN, Bertolami A, Pereira AC, Lottenberg AM, Sposito AC, Chagas ACP, Casella AF, Simao AF, Alencar ACF, Caramelli B, Magalhaes CC, Negrao CE, Ferreira C, Scherr C, Feio CMA, Kovacs C, Araujo DB, Magnoni D, Calderaro D, Gualandro DM, Mello EPJ, Alexandre ERG, Sato EI, Moriguchi EH, Rached FH, Santos FCD, Cesena FHY, Fonseca FAH, Fonseca H, Xavier HT, Mota ICP, Giuliano ICB, Issa JS, Diament J, Pesquero JB, Santos JED, Faria JRN, Melo JXF, Kato JT, Torres KP, Bertolami MC, Assad MHV, Miname MH, Scartezini M, Forti NA, Coelho OR, Maranhao RC, Santos RDDF, Alves RJ, Cassani RL, Betti RTB, Carvalho T, Martinez T, Giraldez VZR and Salgado WF. Atualização da Diretriz Brasileira de Dislipidemias e Prevenção da Aterosclerose – 2017. Arq Bras Cardiol. 2017;109(1):1-76.

7. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/ APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;73(24):e285-e350.

8. ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS, European Heart Journal (2019) 00, 1-78.

9. Cannon CP, Blazing MA, Giugliano RP, McCagg A, White JA, Theroux P, et al; IMPROVE-IT Investigators. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med. 2015;372(25):2387-97.

10. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. N Engl J Med. 2017;376(18):1713-22.

11. Schwartz GG, Bessac L, Berdan LG, Bhatt DL, Bittner V, Diaz R, et al. Effect of alirocumab, a monoclonal antibody to PCSK9, on long-term cardiovascular outcomesfollowing acute coronary syndromes: rationale and design of the ODYSSEY outcomes trial. Am Heart J. 2014 Nov;168(5):682-9.

12. Schmidt A, Moreira HT, Volpe GJ, Foschini VB, Lascala TF, Romano MMD, et al. Perfil de Prescrição de Estatinas e de Níveis Lipêmicos em Ambulatórios de Hospital Terciário Público. Arq Bras Cardiol. 2021; 116(4):736-741.

13. Cesena FHY, Valente VA, Santos RD, Bittencourt MS. Cardiovascular Risk and Statin Eligibility in Primary Prevention: A Comparison between the Brazilian and the AHA/ACC Guidelines. Arq Bras Cardiol. 2020 Sep;115(3):440-449.

14. Santos RD, Gagliardi AC, Xavier HT, Casella Filho A, Araújo DB, Cesena FY, Alves RJ et al. Sociedade Brasileira de Cardiologia. I Diretriz Brasileira de Hipercolesterolemia Familiar (HF). Arq Bras Cardiol. 2012;99(2 Supl. 2):1-28.

15. Ribeiro RA, Duncan BB, Ziegelmann PK, Stella SF, Vieira JL, Restelatto LM and Polanczyk CA. Cost-effectiveness of high, moderate and low-dose statins in the prevention of vascular events in the Brazilian public health system. Arq bras cardiol. 2015;104:32-44.

16. Schubert J, Lindahl B, Melhus H, Renlund H , Leosdottir M, Yari A, Ueda P, James S, Reading SR, Dluzniewski PJ, Hamer AW, Jernberg T, Hagström E.. Low-density lipoprotein cholesterol reduction and statin intensity in myocardial infarction patients and major adverse outcomes: a Swedish nationwide cohort study. Eur Heart J. 2021;42(3):243-252.

Sixteen Years of Heart Transplant in an Open Cohort in Brazil: Analysis of Graft Survival of Patients using Immunosuppressants

Natália Cristina Cardoso Freitas,[1] Mariangela Leal Cherchiglia,[2] Charles Simão Filho,[3] Juliana Alvares-Teodoro,[1] Francisco de Assis Acurcio,[1] Augusto Afonso Guerra Junior[1]

Universidade Federal de Minas Gerais - Faculdade de Farmácia - Departamento de Farmácia Social,[1] Belo Horizonte, MG - Brazil

Universidade Federal de Minas Gerais - Faculdade de Medicina - Departamento de Medicina Preventiva e Social,[2] Belo Horizonte, MG - Brazil

Universidade Federal de Minas Gerais - Faculdade de Medicina - Departamento de Cirurgia,[3] Belo Horizonte, MG – Brazil

Abstract

Background: **Heart transplant is the main therapeutic alternative for advanced heart failure patients. Several risk factors affect these patients' survival; however, few studies about the topic are available in Brazil.**

Objectives: **To review the survival rates of heart transplant patients in the Brazilian Public Health System (Sistema Único de Saúde - SUS) between 2000 and 2015.**

Methods: **This is a non-concurrent, open cohort study, involving cardiac transplant patients in Brazil. The cumulative survival probability was estimated by the Kaplan-Meier curve, and the curve comparison was done using the Log-Rank test. The Cox model was used to calculate the Hazard-Ratio (HR). Analyses were conducted at the 95% confidence level.**

Results: **The heart transplant survival rate median in Brazil, during the period, was 8.3 years. Each additional year in the recipient's age, the occurrence of infections, and the performance of the surgical procedure in the South Region were associated with a higher risk of graft loss. A higher use ratio of immunosuppressants mycophenolate and azathioprine acted as a protection factor.**

Conclusions: **The analyses conducted provide the first information about the median survival time in heart transplant patients in Brazil. The difference noticed among the geographical regions may be related to the different treatment protocols adopted in the country, especially in the early 2000s. The rate of mycophenolate and azathioprine use as a protection factor suggests that, despite the absence of differences among therapeutic strategies, use of these drugs may favor survival of certain patients. The study provides robust epidemiological data, which are relevant for public health. (Arq Bras Cardiol. 2021; 116(4):744-753)**

Keywords: **Heart Transplantation/trends; Cyclosporine/therapeutic use; Survival; Immunosuppresive Agents; Epidemiology.**

Introduction

Heart transplant (HT) is the main therapeutic alternative for patients diagnosed with advanced heart failure (HF) that is refractory to optimized clinical and surgical treatment, and its main purpose is to improve these individuals' survival and quality of life.[1] After transplantation, the extended use of immunosuppressive therapy schemes for transplant maintenance. Although current recommendations allow for the combination and use of several drugs, triple schemes, including corticosteroids, calcineurin inhibitors and antiproliferative agents, remain widely recommended by guidelines and adopted in healthcare services.[2]

Mailing Address: Natália Cristina Cardoso Freitas •
Universidade Federal de Minas Gerais - Faculdade De Farmácia - Dep. Farmácia Social - Avenida Presidente Antônio Carlos, 6627. Postal Code 31270-901, Pampulha, Belo Horizonte, MG – Brazil
E-mail: nccfreitas@gmail.com
Manuscript received February 13, 2020, revised manuscript June 23, 2020, accepted August 16, 2020

DOI: https://doi.org/10.36660/abc.20200117

After the introduction of cyclosporine in the 1980s, the number of heart transplants and survival rates have progressively increased globally. Several risk factors, however, still affect HT survival, among which, recipient and donor demographics, clinical variables, such as HF cause, maintenance therapy strategies adopted, and the incidence of post-transplant complications.[3,4]

Brazil has one of the largest public health systems for transplant in the world, and nearly all procedures are performed by the Unified Health System (SUS). Currently, the country stands out in Latin America and it is considered to be a reference in HT in Chagas disease cases.[5] HT and monitoring of transplanted patients, from the pre-operation procedures to the supply of post-transplant immunosuppressants, are among the thirty most expensive therapies provided to the Brazilian population by the SUS, which is responsible for approximately 96% of the HT procedures performed in the country.[6]

Unlike other countries, however, few studies on HT survival are available in Brazil. Data are scarce and diffuse and, as a result, there is no robust information regarding graft survival and its respective risk factors for the Brazilian population. In this context, the purpose of the present study is to analyze

the survival of patients who underwent HT in the Brazilian SUS, between the years 2000 and 2015, with the records of immunosuppressive scheme use.

Methods

This is a non-concurrent, open cohort study, involving patients who underwent HT in the Brazilian SUS. This cohort study was developed by means of deterministic and probabilistic record linkage – a method used to integrate and unify data from a single patient, originating from different health information systems – of the different SUS administrative data bases: SUS Hospital Information System (SIH/SUS), Outpatient Information System (SIA/SUS) and Mortality Information System (SIM).[7] The study included patients who had undergone HT in SUS, between 01/01/2000 and 12/31/2014. The transplant record date was defined as the date the patient was added to the cohort, and a minimum 12-month monitoring period was defined, so that monitoring ended on 12/31/2015. Patients added during this first phase underwent, initially, the general survival assessment for HT in Brazil.

After that, a cohort was extracted for adult patients, to whom the following previous cohort exclusion criteria were applied: age under 18 years; individuals who underwent multiple transplantation; individuals whose first record in the cohort was that of a retransplant; and individuals for whom the database did not exhibit any records of immunosuppressant use.

Statistical analysis

Descriptive analysis of the variables used in the study and survival analysis were conducted.

Descriptive statistical analysis was conducted for all variables. Categorical variables were analyzed by means of absolute and relative frequency distribution: gender, age group, geographical region where the transplant was conducted, primary HF diagnosis, median cardiovascular disease period prior to the transplant ≥ 17 months, comorbidities/complications developed after the transplant, and immunosuppressive therapy. Each drug use time ratio, up to the event or censoring, for each patient in the cohort, was analyzed by median and interquartile range. These measures were also presented for general age of the adult population.

Survival analyses used the following parameters: the event, defined as graft loss and represented, in this study, by the occurrence of death or retransplant; informative censoring, considered to be the date of the last record regarding immunosuppression; and right censoring, that is, study interruption represented by the monitoring end date (12/31/2015).

The Kaplan–Meier estimator was used to determine the cumulative survival probability of graft survival in patients included in both cohorts. Differences among the curves were compared by the Log-Rank test. Variables were assessed individually, to determine the effect each one of them on survival, and those that exhibited a p-value<0.20 were added to the final multivariate model. Cox's proportional hazards semi-parametric model was used to calculate the Hazard-Ratio (HR) for these univariate and multivariate analyses. Schoenfeld residuals test was used to determine the adjustment and hazard ratio in the final model. All analyses were conducted considering a 95% confidence interval.

Statistical analyses were performed using the Foundation for Statistical Computing' software "R", version 3.6.0.

This study was approved by the Minas Gerais Federal University Committee on Research Ethics (CAAE - 16334413.9.0000.5149).

Results

A total of 2,197 HT patients in Brazil, between 2000 and 2014, were identified, mostly males (70.7%), among which 88.9% (n=1,954) were adults, and 11.1% (n=243) were under 17 years of age. The cohort survival analysis showed rates of 70.9% (69.0 – 72.9) at one year, 59.5% (57.1 – 61.9) at five years, and reaching 45.1% (41.4 – 49.1) at ten years, and 29.1% (23.6 – 35.9%) at the end of the range (13.6 years). The HT survival rate median in the country, during the period, reached 8.3 years (Figure 1).

By comparing the two age groups – adults and teenagers under 17 years of age – a statistically significant difference between them is observed (p=0.003), revealing adults have a slightly lower survival rate. The same difference is observed in the comparison by gender, in which male patients exhibit a lower survival rate after HT (p=0.01).

As the main object of this study, a cohort of adult patients (over 18 years of age) was selected, initially including 1,954 patients. Among these patients, five were excluded, as they had been added to the cohort due to heart retransplant, six were excluded, as they had had multiple transplants, and 740 patients were excluded, as there were no records of medication use in the database. Among the latter, death records were identified for 456, and the remaining 284 are believed to have obtained the immunosuppressants from the supplementary healthcare system and/or at their own expenses. Therefore, 1,203 patients were included in the study.

Median survival rate for this population – adult patients using immunosuppressive schemes – was 11.1 years. Survival rates at one, five and ten years were 89.8% (88.1 – 91.6), 75.9% (73.1 – 78.8) and 57.0% (52.1 – 62.3), respectively.

Among the 1,203 patients included in the study, the majority was male (73.2%), with an average age of 48 years (38 – 56). For 69.1% of these patients (n=831), it was not possible to identify exactly the primary condition that led to the onset of HF, as the first record in the database was the condition itself. Ischemic cardiopathies appear as the second most frequently reported cause, corresponding to 14.1%, while other causes and congenital malformations were the least frequent causes, corresponding to 0.3 and 1.7 of the records, respectively (Table 1).

Few records were checked for the comorbidities that took place after transplant, among which: arterial hypertension (11.1%), infections (3.7%), dyslipidemia (4.0%), and neoplasia (0.9%) (Table 1). No records were found for diabetes, chronic renal failure, or osteoporosis.

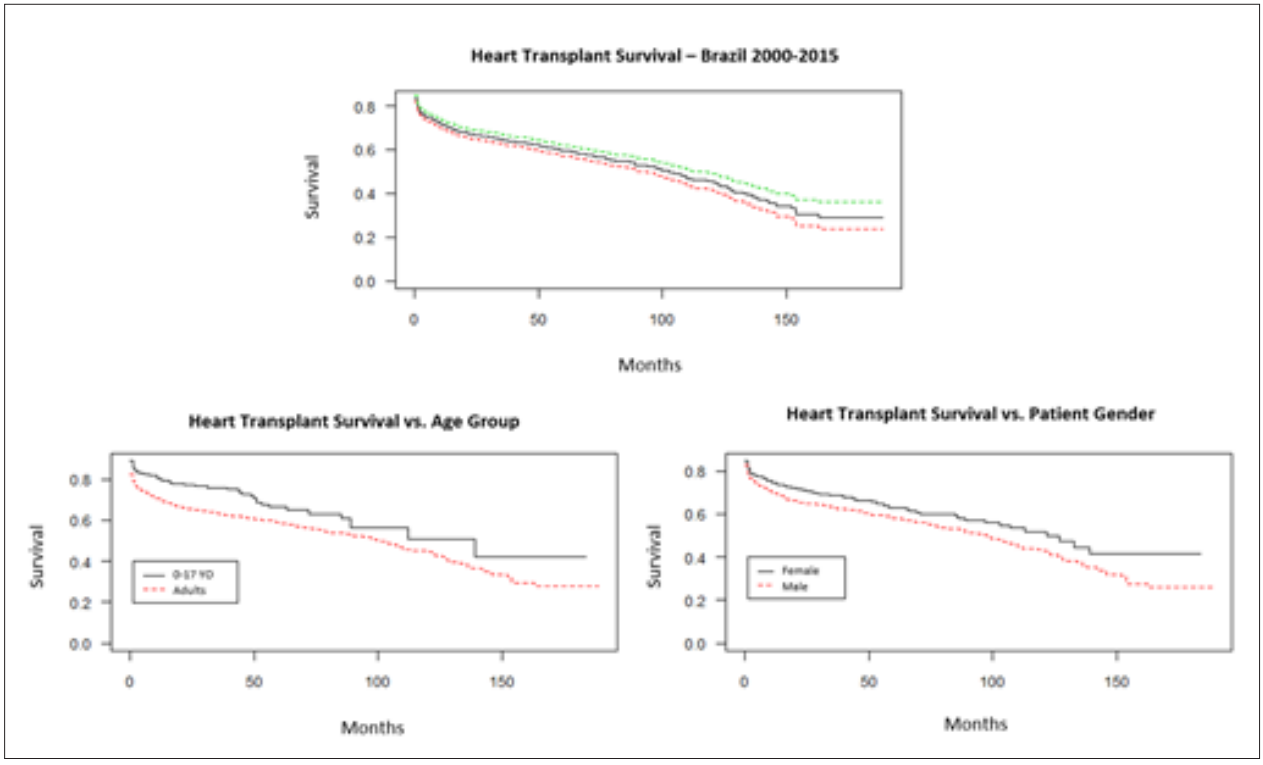


Figure 1 – *Graft survival of heart transplant patients in Brazil between 2000 and 2015. Note: the green and red broken lines in this figure's first chart represent, respectively, the upper and lower limits for the confidence interval (95%)*

Most of the transplant surgeries were performed in the Southeast region (55.9%), South (21.5%) and Northeast (18.5%) (Table 1), and statistically significant differences were observed in the survival rates of patients subjected to the procedure in these regions. The Northeast and Southeast regions exhibited higher survival rates (p= 0.02 and p= 0.01, respectively), while the South region exhibited rates lower than the national average (p<0.0001). The Central-West and North regions have not exhibited significant differences (Figure 2).

Among the different immunosuppressive schemes, the use of cyclosporine associated with mycophenolate was the most frequently first-choice therapy scheme used (58.4%), followed using mycophenolate in monotherapy (18.4%), and by the association between cyclosporine and azathioprine (11.9%). The use of tacrolimus as a calcineurin inhibitor as first line treatment was incipient during this period, as only 3.3% of the individuals started their treatment with it, whereas mycophenolate was the most frequently used antiproliferative agents, being present in approximately 81% of the therapy schemes (Table 2).

Stratification of the use of first choice immunosuppressive schemes by region allowed for observing that the use of cyclosporine and azathioprine was proportionally higher in the country's South region (27.9%), corresponding to approximately 2.3 times the national average. Nevertheless, the association of cyclosporine and mycophenolate was the most frequently used therapy scheme in all regions (Table 3).

No statistically significant differences (p=0.6) were observed upon evaluating patient survival based on the immunosuppressive scheme initially used (Figure 3).

The median of immunosuppressant use over the period was 83.3% for mycophenolate (65.7 – 95.2), 71.1% for cyclosporine (38.5 – 91.7), 38.2% for azathioprine (11.5 – 66.8), 26.0% for tacrolimus (8.3 – 47.2), 15.0% for sirolimus (4.8 – 34.7) and 7.1% for everolimus (2.4 – 28.8).

Univariate analysis of potential risk factors for graft survival revealed a higher risk associated with male patients (HR = 1.342; CI 95% 1.02 – 1.767), with an additional year in the recipient's age (HR = 1.01; CI 95% 1.003 – 1.023), with the surgery being performed in the South region of Brazil (HR = 1.784; CI 95% 1.407 – 2.262), with the median cardiovascular (CVD) time prior to the transplant being higher than 17 months (HR = 1.389; CI 95% 1.067 – 1.807), with the development of post-transplant infections (HR = 1.702; CI 95% 1.012 – 2.861), and with a higher ratio of azathioprine use during the monitoring period (HR = 1.769; CI 95% 1.125 – 2.783) (Table 4).

Conversely, the following acted as survival protection factors, surgeries being performed in the Northeast (HR = 0.688; CI 95% 0.499 – 0.950) and Southeast (HR = 0.758; CI 95% 0.607 – 0.945) regions; and having a higher ratio of mycophenolate (HR = 0.431; CI 95% 0.311 – 0.598) and tacrolimus (HR = 0.273; CI 95% 0.092 – 0.812) use (Table 4).

Primary HF causes and the first-choice immunosuppressant schemes exhibited significant results.

Multivariate analysis showed that each additional year in the recipient's age, the occurrence of infections after the

Table 1 – Demographics of the study population

Characteristics	Total (n = 1203)	
	n	%
Geographical region where transplant was performed		
Central-West	43	3.6
Northeast	222	18.5
North	8	0.7
Southeast	672	55.9
South	258	21.4
Gender		
Female	323	26.8
Male	880	73.2
Age group (years of age)		
18 - 25 years of age	54	4.5
26 - 35 years of age	179	14.9
36 - 45 years of age	271	22.5
46 - 55 years of age	392	32.6
56 - 65 years of age	278	23.1
> 65 years of age	29	2.4
Causes of heart failure		
Cardiomyopathies	76	6.3
Undefined cardiomyopathies	831	69.1
Ischemic cardiomyopathies	170	14.1
Congenital malformations	20	1.7
Other cardiac conditions	4	8.5
Other causes	102	0.3
Median period with previous cardiovascular disease		
Median time lower than or equal to 17 months	434	36.1
Median time greater than 17 months	427	35.5
Comorbidities/post-transplant complications		
Dyslipidemia	48	4.0
Arterial hypertension	134	11.1
Infections	45	3.7
Neoplasia	11	0.9
Events		
Censoring	891	74.1
Death	307	25.5
Retransplant	5	0.4

transplant, and the performance of the surgical procedure in the South region were associated with a higher risk of graft loss. However, a higher use ratio of immunosuppressants mycophenolate and azathioprine acted as a protection factor (Table 5). The model was verified by the Schoenfeld residuals method, and it demonstrated a risk proportionality for all variables, as well as linear correlation to time.

Discussion

The study is designed to evaluate underexplored and disseminated data about HT in Brazil. Analyzes performed allow for providing initial information about the median survival time for this type of transplant in the country, estimated at 8.3 years, between 2000 and 2015.

Survival probabilities described for the first (70.9%) and the fifth (59,5%) years of monitoring, are slightly lower than those described by the Brazilian Association of Organ Transplantation (ABTO), the only agency that currently publicizes such data in the country, which provides, comparatively, the rates of 74% and 64% for the same monitoring times.[8] Data provided by ABTO, however, come from a historical series started in 2010; therefore, more recent than the one used in this study, for which an important increase is expected for survival estimates worldwide, considering the improvement of transplantation teams and the arrival of new drugs in the market.[9]

Data from the International Society for Heart and Lung Transplantation (ISHLT) show that median HT survival worldwide was 8.6 years in the period between 1982 and 1991, whereas in the period between 2002 and 2008 this number reached 12.2 years. Survival rates at one and five years are also higher than the Brazilian rates: 81 and 69%, respectively. ISHLT data, however, originate primarily from European and North American countries, which have quite different sociodemographic and clinical characteristics, as well as the health systems, from those in Brazil.[4]

Although it was impossible to clearly define the main HF causes, the occurrence of ischemic cardiomyopathies as the second most frequent cause is in agreement with several studies performed that indicate this as one of the main HF causes worldwide.[9-11] A significant number of Chagas disease patient records was expected, given this is an endemic disease in the country and it is known to be related to the occurrence of HF. Other conditions, such as hypertensive disease, were also expected.[12] Such inconsistency is believed to be associated with the fact that early treatment of these patients takes place at primary health care centers - whose records are scarce and are not reached by this study's database - so that, when medium and high complexity assistance levels are reached, patients face advanced HF, and this is their first record.

The same applies to comorbidity records that could not have been checked in full. Hypertension and dyslipidemia records, however, provide important data, as such conditions are commonly associated with the use of cyclosporine, when compared to tacrolimus, more frequently associated with diabetes.[13-17] In addition, as provided in table 1, the use of cyclosporine was significantly greater than the use of tacrolimus in the studied population. The use of tacrolimus for HT in Brazil, it should be noted, however, is still done off-label, and this prevented this drug from being widely available at the national level until 2015, when it was added, by the National Committee for Health Technology Incorporation (CONITEC) to the list of drugs provided by the SUS, along with everolimus and sirolimus.[6]

Conversely, the analyses conducted demonstrated that no differences in effectiveness have been detected among the therapy schemes used. Several studies corroborate these data,

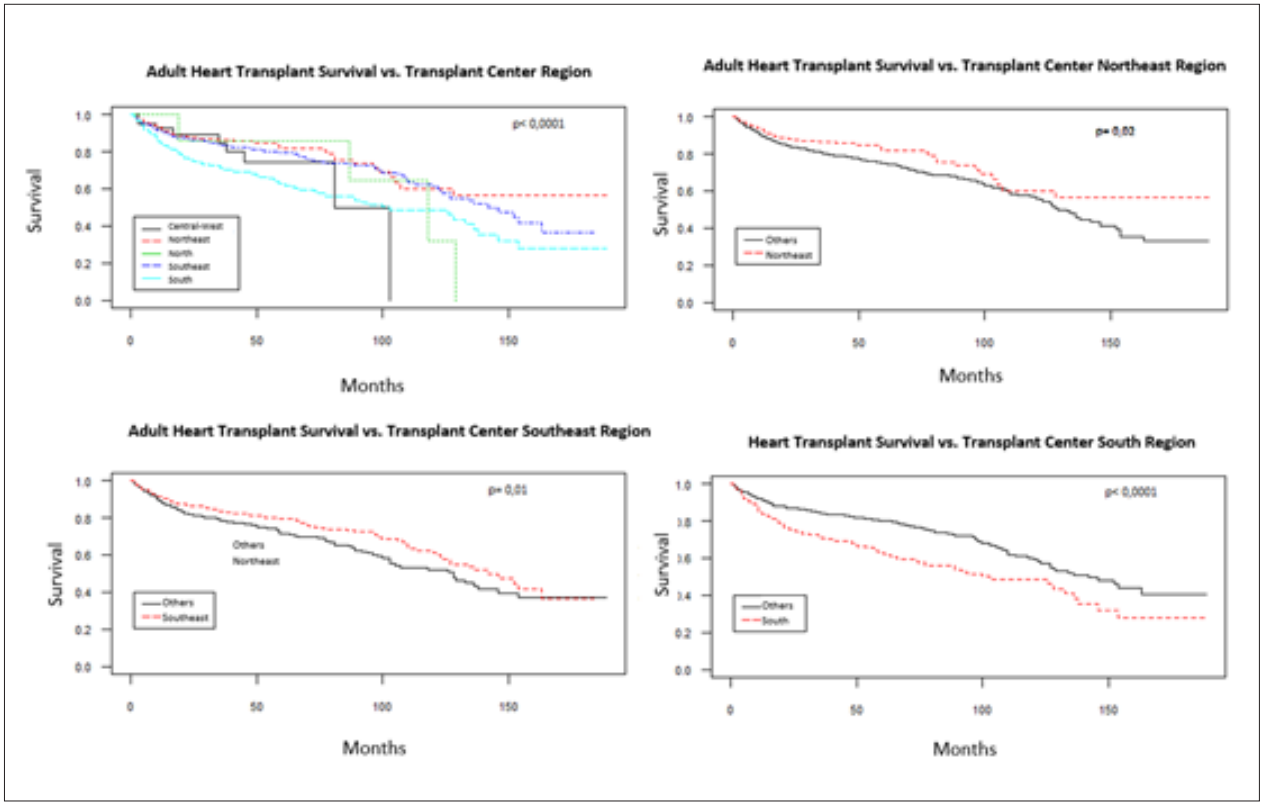


Figure 2 - *Graft survival of adult heart transplant patients in Brazil between 2000 and 2015 by region.*

Table 2 – First choice immunosuppressant schemes used by the study population

Main immunosuppressant schemes Start of cohort	N	%	%accumulated*
Cyclosporine + Mycophenolate	702	58.4%	58.4%
Mycophenolate (monotherapy)	221	18.4%	76.7%
Cyclosporine + Azathioprine	143	11.9%	88.6%
Cyclosporine (monotherapy)	52	4.3%	92.9%
Mycophenolate + Tacrolimus	34	2.8%	95.8%
Subtotal	**1152**	**95.8%**	**95.8%**
Other immunosuppressant schemes Start of cohort			
Azathioprine (monotherapy)	22	1.8%	97.6%
Mycophenolate + Sirolimus	15	1.2%	98.8%
Tacrolimus (monotherapy)	3	0.2%	99.1%
Azathioprine + Cyclosporine + Mycophenolate	2	0.2%	99.3%
Azathioprine + Tacrolimus	2	0.2%	99.4%
Cyclosporine + Sirolimus	2	0.2%	99.6%
Sirolimus (monotherapy)	2	0.2%	99.8%
Azathioprine + Sirolimus	1	0.1%	99.8%
Mycophenolate + Cyclosporine + Sirolimus	1	0.1%	99.9%
Mycophenolate + Sirolimus + Tacrolimus	1	0.1%	100.0%
Subtotal	**51**	**4.2%**	**100%**
Total	**1203**	**100%**	**100%**

**sum of each scheme percentage line by line.*

Table 3 – First choice immunosuppressant schemes used by the study population stratified by geographical region

Transplant Center Region	Azathio + Cyclos	Cyclos (monotherapy)	Cyclos + Mycophe	Mycophe (monotherapy)	Mycophe + Tacrol	Other schemes	Overall total
	n (%)						
Central-West	5(11.6)	1(2.3)	17(39.5)	8(18.6)	1(2.3)	11(25.6)	43(100.0)
Northeast	12(5.4)	7(3.1)	133(59.9)	58(26.1)	1(0.4)	11(4.9)	222(100.0)
North	0(0.0)	0(0.0)	8(100.0)	0(0.0)	0(0.0)	0(0.0)	8(100.0)
Southeast	54(8.0)	18(2.7)	410(61.0)	138(20.5)	28(4.2)	24(3.6)	672(100.0)
South	72(27.9)	26(10.1)	134(51.9)	17(6.6)	4(1.5)	5(1.9)	258(100.0)
Overall total	143(11.9)	52(4.3)	702(58.4)	221(18.4)	34(2.8)	51(4.2)	1203(100.0)

Azathio: azathioprine; Cyclos: cyclosporine; Mycophe: mycophenolate; Tacrol: tacrolimus.

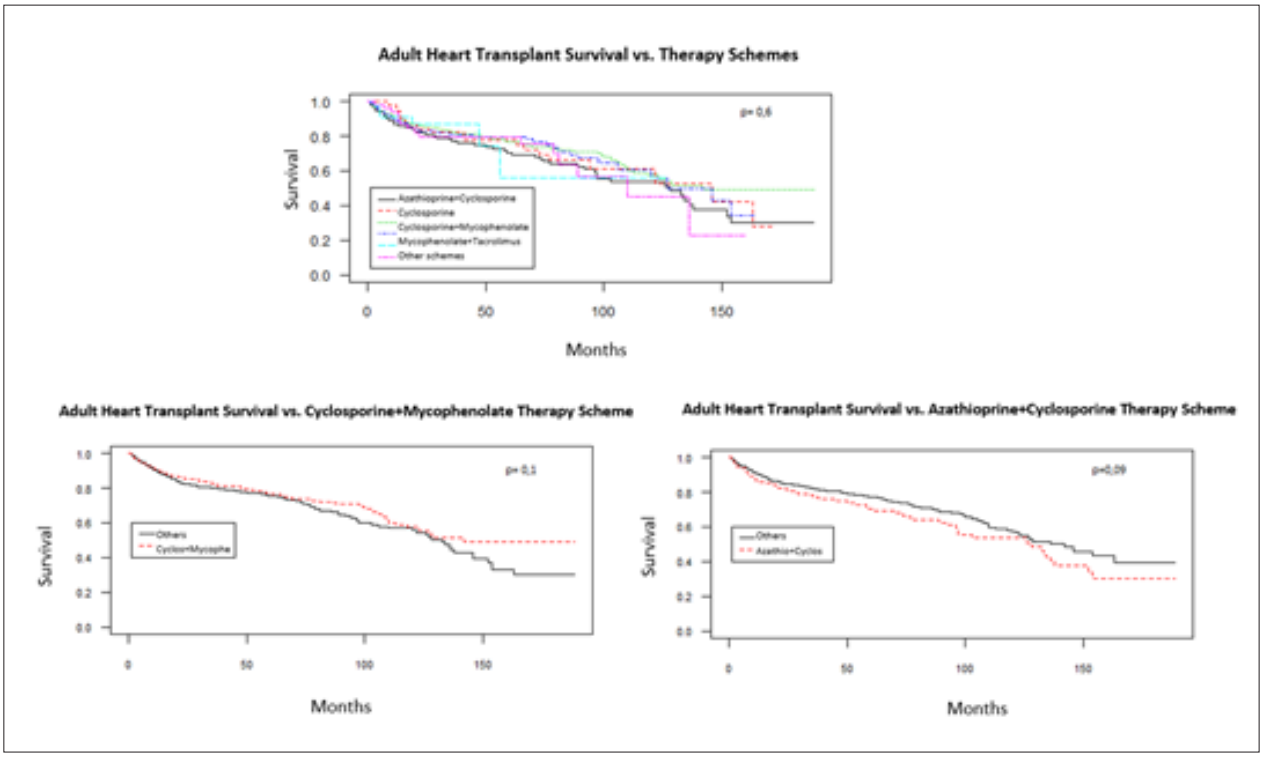


Figure 3 – Graft survival of adult heart transplant patients in Brazil between 2000 and 2015 by immunosuppressive scheme.

especially in relation to the comparison between cyclosporine and tacrolimus; although some studies indicate a lower occurrence of rejection when tacrolimus is used, there is no evidence of its superiority for patient survival purposes. In clinical practice, however, there has been a significant increase in the use of tacrolimus for the past years, which may also take place in Brazil after its addition to the list of drugs provided by the SUS.[1,13-17]

The high rates of mycophenolate use observed in the study also follow a global trend and, although no differences were detected among the therapeutic combinations, some studies suggest mycophenolate has a slightly superior effectiveness in relation to azathioprine, as observed in the Kaplan-Meier curves presented in this study, despite the absence of statistically significant results.[18-22] In the Brazilian context, it is noteworthy that national studies indicate unfavorable results with the use of mycophenolate in Chagas disease patients, due to the high rates of disease reactivation after transplantation.[23-25]

Nevertheless, the rate of mycophenolate and azathioprine use has proved to be a survival protection factor in the multivariate model, suggesting that, despite the absence of differences among therapeutic strategies used initially, the use of these drugs for a longer period, appears to contribute to the survival of certain patients.

Although the rate of azathioprine use appeared as a risk factor in the univariate analysis (Table 4), it appears as a protection factor in the final model, within the significance

Table 4 – Graft loss hazard ratio - univariate analysis

Variable	Total (n = 1203)	
	HR (CI 95%)	p
Geographical region where transplant was performed		
Central-West	1.128 [0.580 - 2.194]	0.7
Northeast	0.688 [0.499 - 0.950]	0.02
North	1.489 [0.555 - 3.997]	0.4
Southeast	0.758 [0.607 - 0.945]	0.01
South	1.784 [1.407 - 2.262]	<0.001
Gender, Male	1.342 [1.019 - 1.767]	0.04
Age	1.013 [1.003 - 1.023]	0.01
Causes of heart failure		
Cardiomyopathies	0.962 [0.617 - 1.498]	0.9
Undefined cardiomyopathies	1.144 [0.899 - 1.457]	0.3
Ischemic cardiomyopathies	0.950 [0.681 - 1.323]	0.8
Congenital malformations	0.349 [0.087 - 1.404]	0.1
Other cardiac conditions	3.67 [0.912 - 14.77]	0.05
Other causes	0.863 [0.593 - 1.256]	0.4
Median CVD time prior to transplant	1.389 [1.067 - 1.807]	0.01
Onset of post-transplant comorbidities		
Dyslipidemia	0.919 [0.473 - 1.786]	0.8
Arterial hypertension	1.270 [0.896 - 1.800]	0.2
Infections	1.702 [1.012 - 2.861]	0.04
Neoplasia	1.363 [0.339 - 5.490]	0.7
First choice immunosuppressant schemes		
Cyclosporine	1.057 [0.664 - 1.683]	0.8
Cyclosporine + Azathioprine	1.295 [0.964 - 1.741]	0.09
Cyclosporine + Mycophenolate	0.843 [0.675 - 1.054]	0.1
Mycophenolate	0.998 [0.739 - 1.347]	1.0
Mycophenolate + Tacrolimus	0.956 [0.426 - 2.149]	0.9
Other schemes	1.162 [0.692 - 1.953]	0.6
Ratio of immunosuppressant use in the segment		
Azathioprine	1.769 [1.125 - 2.783]	0.01
Cyclosporine	1.244 [0.904 - 1.711]	0.2
Everolimus	0.051 [0.000 - 13.99]	0.3
Mycophenolate	0.431 [0.311 - 0.598]	<0.001
Sirolimus	0.699 [0.199 - 2.462]	0.6
Tacrolimus	0.273 [0.092 - 0.812]	0.02

Table 5 – Graft loss hazard ratio: multivariate analysis

Variable	HR (CI 95%)	p
Age (additional year)	1.014 [1.004 - 1.025]	0.006
Post-transplant infections	1.912 [1.136 - 3.243]	0.015
South Region	1.592 [1.240 - 2.044]	<0.001
Mycophenolate use ratio	0.353 [0.224 - 0.557]	<0.001
Azathioprine use ratio	0.518 [0.272 - 0.988]	0.046

limit and close to the ineffective range (namely: HR= 1.00 and p>0.05). This fact may be justifiable, considering that, in univariate analysis, medication use periods are compared individually, that is, whether patients have used the medication in question or not. In multivariate analysis, however, the use of azathioprine is considered individually, as well as the use of all drugs in different combinations and along with other variables. Therefore, it is reasonable to consider that, under these conditions, azathioprine does not necessarily represent a risk to patient survival, considering that other factors may pose higher death risks than the medication use. The fact that groups with different characteristics and needs will benefit from different schemes must be also taken into account, as this appears to be the case of Chagas disease patients, who benefit from azathioprine use.

Furthermore, upon assessing the use of therapy schemes by geographical region, the South region exhibits a higher azathioprine use percentage when compared to all other regions. In addition, transplantation procedures being performed in this region also appear to affect survival, resulting in its characterization as a risk factor in the multivariate model, Higher azathioprine use percentage was also observed mainly in the first years of the monitoring period, between 2000 and 2004. From then on, this drug use rate in the South region is close to the rate observed in other geographical regions. These data suggest that the difference observed in survival rates among the geographical regions may be related to treatment protocols adopted in the South region, considering that Brazil does not have a unified clinical protocol for HT, mainly during the early 2000s, when the study and, consequently, evidence of comparison between azathioprine and mycophenolate were recent.

Brazil is notably a country of continental proportions with significant differences among its five geographical regions; therefore, these discrepancies may also be related to other factors, such as, illness severity of patients subject to transplantation, agility in organ transportation, physical and human resource structure in the transplantation centers, transplantation team qualification, in addition to clinical guidelines and protocols adopted for handling donor and recipient, among other conditions. Other data, therefore, are required to clarify all of these conditions, as well as how they affect patient survival.

The multivariate model also showed that infections occurred after transplantation and the additional year of age were risk factors to patient survival. Infections are known to be one of the main causes of death after HT, especially during the first year. Similarly, recipient age is related to survival, and a directly proportional increase in mortality rates is observed in short and long terms.[1,9]

The 'gender' demographic variable, admittedly associated with higher risk for survival in HT, was not significant in the final model for the studied population. Nevertheless, this fact is believed to be associated with a significant difference in size among the groups, as the number of male patients was approximately 2.5 times the number of female patients, considering that other studies suggest significantly higher survival rates in women.[9]

Difficulties in observing relevant results for clinical variables, such as median CVD time prior to the transplant, HF cause and post-transplantation comorbidities, are related to the main limitation in this study, which is the use of data originating from administrative databases. In general, such databases provide no clear and easily identifiable records of clinical information, as they were not built for these purposes. Therefore, the assessment of important variables related to donors or to the patients' clinical condition before and after transplantation, and which may directly affect their survival rates or the regional differences observed, could not be reviewed. In addition, information available may exhibit inconsistencies and omissions, also due to the retrospective nature of the study.

Conclusions

This study, with a nationwide reach, presents robust data, which have great relevance for the public health system, about the survival of HT patients monitored by the SUS, potentially useful for the development of guidelines and protocols.

The general survival rate median for HT patients in Brazil, between 2000 and 2015, was 8.3 years, whereas for adult individuals with records of using immunosuppressant provided by the SUS, the estimated survival period was 11.1 years. For this population, the study demonstrated that age, the occurrence of infection after transplantation, and having had surgery in the South region acted as risk factors to survival in the period studied.

These results provide unpublished epidemiological data on HT in Brazil, which may be publicized to contribute with the public health system, as well as with the conduct adopted and for these patients' care.

Author contributions

Conception and design of the research: Freitas NCC, Cherchiglia ML, Simão Filho C, Acurcio FA, Guerra Junior AA; Acquisition of data, Analysis and interpretation of the data and Statistical analysis: Freitas NCC, Guerra Junior AA; Writing of the manuscript: Freitas NCC; Critical revision of the manuscript for intellectual content: Freitas NCC, Cherchiglia ML, Simão Filho C, Alvares-Teodoro J, Acurcio FA, Guerra Junior AA.

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 article is part of the thesis of master submitted by Natália Cristina Cardoso Freitas, from Universidade Federal de Minas Gerais - Faculdade de Farmácia - Dep. Farmácia Social.

References

1. Bacal F, Marcondes-Braga FG, Rohde LEP, Xavier júnior JL, De Souza Brito F, Moura LZ, et al. 3ª Diretriz Brasileira de Transplante Cardíaco. Arq Bras Cardiol. 2018; 111(2):230-89.
2. Mangini S, Alves BR, Silvestre OM, Pires PV, Pires LJT, Curiati MNC, et al. Transplante cardíaco: revisão. Einstein. 2015;13(2):310-8. DOI: 10.1590/S1679-45082015RW3154.
3. Castel MA, Roig E, Rios J, Tomas C, Mirabet S, Cardona M, et al. Long-term prognostic value of elevated heart rate one year after heart transplantation. Int J Cardiol.2013;168(3):2003-7.
4. Lund LH, Khush KK, Cherikh WS, Goldfarb S, Kucheryavaya AY, Levvey BJ,. et al. International Society for Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: thirty-fourth adult heart transplant report--2017; Focus Theme: Allograft ischemic time. J Heart Lung Transplant. 2017;36(10):1037-46.
5. Bacal F, Neto JSD, Fiorelli AI, Mejia J, Marcondes-Braga FG, Mangini S, et al. II Diretriz Brasileira de Transplante Cardíaco. Arq Bras Cardiol.2009;94(1 supl.1):e16-e73
6. Brasil. Ministério da Saúde. Secretaria de Ciência, Tecnologia e Insumos Estratégicos. Comissão Nacional de Incorporação de Tecnologias no SUS. Relatório de Recomendação nº 75 – Everolimo, sirolimo e tacrolimo para imunossupressão em transplante cardíaco. Brasília, 2015. Acesso em 26 de maio de 2018. Disponível em: http://conitec.gov.br/images/Relatorios/2016/Relatorio_Everolimo-Sirolimo-Tacrolimo_final.pdf
7. Guerra Junior AA, Pereira RG, Andrade EIG, Cherchiglia M, Dias LV, Ávila JD,et al. Building the National Database of Health Centred on the Individual: Administrative and Epidemiological Record Linkage - Brazil, 2000-2015. Int J Popul Data Sci. 2018;3:3-20.
8. Associação Brasileira De Transplantes De Órgãos. (ABTO). Registro Brasileiro de Transplantes 2018 [Internet]. Ano XXIV, nº4; 2018. Acesso em 21 de setembro 2019. Disponível em: http://www.abto.org.br
9. Khush KK, Cherikh WS, Chambers DC, Goldfarb S, Hayes Jr D, Kucheryavaya AY, et al. The International Thoracic Organ Transplant. International Society for Heart and Lung Transplantation. The Registry of the International Society for Heart and Lung Transplantation: thirty-fifth adult heart transplant report--2018; Focus Theme: Multiorgan Transplantation. 2018;37(10):1155-68.
10. Kemp CD.; Conte JV. The pathophysiology of heart failure. Cardiovasc Pathol.2012;21(5):375-71.
11. Pearse SG.; Cowie MR. Heart failure: classification and pathophysiology. J Med.2014;42(10):556-61.
12. Albuquerque DC, Neto JDS, Bacal F, Rohde LEP, Bernardez-Pereira S, Berwanger O, et al. I Registro Brasileiro de Insuficiência Cardíaca – Aspectos Clínicos, Qualidade Assistencial e Desfechos Hospitalares. Arq Bras Cardiol. 2014; [online].ahead print.
13. xxxxxxTaylor DO, Sharma RC, Kfoury AG, Renlund DG. Increased incidence of allograft rejection in stable heart transplant recipients after late conversion from mycophenolate mofetil to azathioprine. Clin Transpl. 1999;13(4):296-9.
14. Kobashigawa JA, Tobisa JM, Mentzer RM, Valantine HA, Bourged RC, Mehrae MR, et al. Five-Year Results of a Randomized, Single-Center Study of Tacrolimo vs Microemulsion Cyclosporine in Heart Transplant Patients. J Heart Lung Transplant. 2006 Apr;25(4):434-9.
15. Grimm M, Rinaldi M, Yonan NA, Arpesella G, Arizón Del Prado JM, Pulpón LA, et al. Superior prevention of acute rejection by tacrolimo vs. cyclosporine in heart transplant recipients--a large European trial. Am J Transplant. 2006; 6(6):1387-97.
16. Ye F, Ying-Bin X, Yu-Guo W, Hetzer R. Tacrolimo Versus Cyclosporine Microemulsion for Heart Transplant Recipients: A Meta-analysis. J Heart Lung Transplant. 2009 Jan;28(1):58 66. DOI: 10.1016/j.healun.2008.10.004.
17. Penninga L, Møller CH, Gustafsson F, Steinbrüchel DA, Gluud C. Tacrolimo versus cyclosporine as primary immunosuppression after heart transplantation: systematic review with meta-analyses and trial sequential analyses of randomised trials. Eur J Clin Pharmacol.2010;66:1177-87. DOI 10.1007/s00228-010-0902-6.
18. Kobashigawa JA, Miller L, Renlund D, Mentzer R, Alderman E, Bourge R; et al. A randomized active-controlled trial of mycophenolate mofetil in heart transplant recipients. Transplantation. 1998 Aug;66(4):507-15.
19. Taylor DO, Barr ML, Radovancevic B, Renlund DG, Mentzer RM Jr, Smart FW; et al. A randomized, multicenter comparison of tacrolimus and cyclosporine immunosuppressive regimens in cardiac transplantation: decreased hyperlipidemia and hypertension with tacrolimus. J Heart Lung Transplant. 1999;18(4):336-45.
20. Kobashigawa JA, Meiser BM. Review of major clinical trials with mycophenolate mofetil in cardiac transplantation. Transplantation. 2005; 80(2 Suppl): S235-S243.
21. Seebacher G, Weigel G, Griesmacher A, Mallinger R, Zuckermann A, Grimm M, et al. One and a Half Years of Experience With Mycophenolate Mofetil (Cellcept) in Cardiac Transplantation: A Prospective, Randomized Study. Transplant Proc. 1999;31(8):3291-3.
22. Eisen HJ, Kobashigawa JA, Keogh A, Bourge R, Renlund D, Mentzer R. Three year results of a randomized, double-blind, controlled trial of mycophenolate mofetil versus azathioprine in cardiac transplant recipients. J Heart Lung Transplant. 2005; 24(5):517-25.
23. Bacal F, Silva CP, Bocchi EA, Pires PV, Moreira LF, Issa VS, et al. Mycophenolate mofetil increased Chagas' disease reactivation in heart transplanted patients: comparison between two different protocols. Am J Transplant. 2005; 5(8):2017-21.
24. Bestetti RB, Souza TR, Lima MF, Theodoropoulos TA. D. Effects of a mycophenolate mofetil-based immunosuppressive regimen in Chagas' heart transplant recipients. Transplantation. 2007;84(3):441-2.
25. Bacal F, Silva CP, Pires PV. Transplantation for Chagas disease: an overview of immunosuppression and reactivation in the last two decades. Clin Transplant. 2010;24(2):E29-34

Progress in Heart Transplantation in Brazil: is it Time to Build a National Database?

Mônica Samuel Avila[1] *and Deborah de Sá Pereira Belfort*[1]

Universidade de São Paulo Faculdade de Medicina Hospital das Clínicas Instituto do Coração,[1] *São Paulo, SP – Brazil*

Short Editorial related to the article: Sixteen Years of Heart Transplant in an Open Cohort in Brazil: Analysis of Graft Survival of Patients using Immunosuppressants

Heart transplantation (HT) is the therapy of choice for advanced heart failure.[1] Survival has greatly improved since the first heart transplant 50 years ago, especially after the introduction of calcineurin inhibitors and better management of complications related to immunosuppression.[2] In Latin America, Brazil is renowned for the high number of HTs performed annually.[3] Despite its importance, reports on survival, immunosuppression and complications of HT are scarce in Brazil.

A retrospective open cohort of HT in Brazil is presented in this issue of Arquivos Brasileiros de Cardiologia.[4] The article shows important data regarding epidemiology, survival and complications of HT recipients between 2000 and 2015. Median survival in this cohort was 8.3 years, and one- and 5-year survival rates were 70.9% and 59.5%, respectively. These results are better than those from 1984 to 1999, when the one- and 6-year survival rates were 66% and 54% respectively,[5] suggesting improvement in post-transplant care. However, this median survival is lower than 12.2-year survival and one- and 5-year survival of 81% and 69% reported by the International Society of Heart and Lung Transplantation (ISHLT),[6] probably due to sociodemographic and economic differences between Brazil and developed countries.

In order to understand the main factors associated with survival rates in Brazil, the authors studied different variables and geographic regions of Brazil. They found that the recipient's older age (HR 1.014 [95%CI: 1.004-1.025], p=0.006), South of Brazil as the location where HT was performed (HR: 1.592 [95%CI: 1.240-2.044], p<0.001), and post-transplant infection (HR: 1.912 [IC 95%: 1.136-3.243], p=0.015) as significant risk factors for graft loss (death or retransplant). Regarding immunosuppressive regimens, antiproliferative drugs were associated with lower mortality, while calcineurin inhibitors showed no impact on survival after HT.

As the data were extracted from three administrative databases, some missing information affected the results: the etiology of heart failure was not clear in 69.1% of cases; the use of corticosteroids was not described; causes of death were also not reported and no data on graft rejection or cardiac allograft vasculopathy were reported. All of these variables are directly related to improvements in HT treatment and survival.[6,7] Also, in the ISHLT 2017 registry, more than 30% of HT recipients deaths worldwide in the first year post-transplant were caused by infectious diseases,[6] while in this cohort only 3.7% of all patients had infections registered. Indeed, infection is the main cause of death in the first year pos-transplant according to the ISHLT.[8]

Such disparities in the data are probably due to the retrospective nature of the research. Some questions remain unanswered, and perhaps a unified national database would help to fulfill these gaps in Brazilian literature. Despite these limitations, this publication certainly increases the knowledge about HT scenario in Brazil, since this is the only recent cohort study correlating survival, immunosuppression, and clinical variables. It also highlights important points such as regional differences, public health problems, and improvement in HT survival in the last decades in Brazil.

Keywords

Heart Failure/surgery; Heart Transplantation/trends; Survival; Immunosupression/complications; Brazil.

Mailing Address: Mônica Samuel Avila •
Universidade de São Paulo Faculdade de Medicina Hospital das Clínicas Instituto do Coração – Av. Dr. Eneas de Carvalho Aguiar, 44. Postal Code 05403-000, São Paulo, SP – Brazil
E-mail: mo_avila@hotmail.com

DOI: https://doi.org/10.36660/abc.20210104

References

1. Marcondes-Braga FG, Vieira JL, Souza Neto JD, Ayub-Ferreira SM, Calado G, Clausell N. et al. Emerging Topics in Heart Failure: Contemporaneous Management of Advanced Heart Failure. *Arq Bras Cardiol*. Dec 2020;115(6):1193-6. doi:10.36660/abc.20201194
2. Stehlik J, Kobashigawa J, Hunt SA, Reichenspurner H, Kirklin JK. Honoring 50 Years of Clinical Heart Transplantation in. *Circulation*. 2018;137(1):71-87. doi:10.1161/CIRCULATIONAHA.117.029753
3. Pêgo-Fernandes PM, Pestana JOM, Garcia VD. Transplants in Brazil: where are we? *Clinics (Sao Paulo)*. 2019;74:e832. doi:10.6061/clinics/2019/e832
4. Freitas NCC, Cherchiglia ML, Simão Filho C, Alvares-Teodoro J,Acurcio FA, Guerra Junior AA. Dezesseis Anos de Transplante Cardíaco em Coorte Aberta no Brasil: Análise de Sobrevivência de Pacientes em Uso de Imunossupressores. Arq Bras Cardiol. 2021; 116(4):744-753.
5. Bocchi EA, Fiorelli A. The Brazilian experience with heart transplantation: a multicenter report. *J Heart Lung Transplant*. 2001;20(6):637-45. doi:10.1016/s1053-2498(00)00235-7
6. Lund LH, Khush KK, Cherikh WS,Goldfarb S, Kucheryavaya AY, Levvey BJ, et al. The Registry of the International Society for Heart and Lung Transplantation: Thirty-fourth Adult Heart Transplantation Report-2017; Focus Theme: Allograft ischemic time. *J Heart Lung Transplant*. 10 2017;36(10):1037-46. doi:10.1016/j.healun.2017.07.019
7. Bacal F, Marcondes-Braga FG, Rohde LEP,Xavier Jr JL, Brito FS, Moura LAZ, et al. 3ª Diretriz Brasileira de Transplante Cardíaco. *Arq Bras Cardiol*. 2018;111(2): 230-89.
8. Khush KK, Cherikh WS, Chambers DC,Harhay MO, Hayes D Jr, Hsich E, et al. The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-sixth adult heart transplantation report - 2019; focus theme: Donor and recipient size match. *J Heart Lung Transplant*. 10 2019;38(10):1056-66. doi:10.1016/j.healun.2019.08.004

Association between Serum Serglycin Levels and St-Segment Elevation Myocardial Infarction

Burcu Ugurlu Ilgın,[1] Emrullah Kızıltunç,[1] Murat Gök,[2] Ender Ornek,[1] Canan Topcuoglu,[3] Mustafa Çetin,[1] Orhan Karayiğit[4]

TC Saglık Bakanlıgı Gazi Mustafa Kemal Devlet Hastanesi – Cardiology,[1] Ankara - Turkey
Cardiology Department, Edirne Provincial Health Directorate Edirne Sultan 1st Murat State Hospital,[2] Edirne - Turkey
Medical Biochemistry Department, Numune Education and Research Hospital,[3] Ankara - Turkey
Cardiology Department, Numune Education and Research Hospital,[4] Ankara - Turkey

Abstract

Background: **It is suggested that serglycin has important functions in fibrin stabilization and inflammation but there is limited information on its clinical value for atherosclerotic heart disease.**

Objective: **The purpose of this study is to find out serum serglycin levels in acute myocardial infarction patients and in the control group individuals; and to investigate the association between serglycin levels with inflammation markers and infarct size markers.**

Methods: **The study population consisted of 75 patients with ST-segment elevation myocardial infarction (STEMI) and 57 patients with normal coronary arteries (NCA) (control group). Patient characteristics, serum serglycin levels, high-sensitivity C-reactive protein (hs-CRP) levels, peak troponin T levels and other biochemical parameters were recorded. A p value <0.05 was considered statistically significant.**

Results: **The control group consisted of individuals who are younger and smoke less than those of the STEMI group. The number of females in the control group was higher than in the STEMI group. Serum serglycin levels were significantly higher in the STEMI group than in control group (102.81±39.42 vs. 57.13±32.25, p<0.001). Correlation analyses revealed a significant positive correlation between serglycin and troponin (Spearman's Rho: 0.419; p<0.001) and between serglycin and hs CRP (Spearman's Rho: 0.336; p<0.001). Multivariate logistic regression analysis demonstrated that serum serglycin levels were independently associated with STEMI. Using a cutoff level of 80,47 μg/L, the serglycin level predicted the presence of STEMI with a sensitivity of 75.7% and specificity of 68.4%.**

Conclusion: **Serum serglycin levels were significantly higher in the STEMI group than in the control group. Serum serglycin levels were positively correlated with both hs CRP levels and troponin levels. (Arq Bras Cardiol. 2021; 116(4):756-762)**

Keywords: **Cardiovascular Diseases; Myocardial Infarction; Atherosclerosis; Coronary Artery Disease; Inflammation; Biomarkers; Serglycin.**

Introduction

Atherosclerotic heart disease is one of the most important causes of death and morbidity all around the world. Chronic vascular inflammation is accepted atherosclerotic plaque formation, but the promoters and drivers of chronic vascular inflammation are still under investigation.[1,2]

Serglycin is an intracellular proteoglycan expressed mostly in neutrophils, lymphocytes, monocytes, macrophages, platelets, megakaryocytes and mast cells,[3] but it can also be produced by certain non-hematopoietic cells like endothelial cells.[4] It is stored in cell vesicles and reacts with mediators such as cytokines, chemokines, growth factors and proteases.[3] There is evidence about the role of serglycin in inflammation and atherogenic-prothrombotic cascades. It was demonstrated that serglycin synthesis and secretion are triggered in human endothelial cells and monocytes by proinflammatory stimulants.[5,6] In another study, it was found that serglycin binds to C1q receptors, and affects fibrin polymerization in fibrin clot formation.[7] Serglycin is one of the ingredients of platelet alfa granules. These granules are involved in platelet activation in response to inflammation, thrombus formation and atherosclerosis.[8]

The aforementioned effects and functions of serglycin lead to high suspicions about the potential relationship between serglycin and atherosclerotic cardiovascular disease, but there is not good evidence. Therefore, this study aimed to investigate serum serglycin levels in ST-segment elevation myocardial infarction (STEMI) patients and to evaluate an association

Mailing Address: Burcu Ugurlu Ilgın •
TC Saglık Bakanlıgı Gazi Mustafa Kemal Devlet Hastanesi – Cardiology - Cardiology Department, Gazi Mustafa Kemal State Hospital, Ankara, Turkey, 06560 Ankara 06560 – Turkey
E-mail: aburcuburcuyum@hotmail.com
Manuscript received August 29, 2019, revised mansucript january 20, 2020, accepted March 16, 2020

DOI: https://doi.org/10.36660/abc.20190554

between serum serglycin levels and prognostic markers of STEMI.

Methods

Study population

We enrolled patients with acute ST-segment elevation myocardial infarction (STEMI) and patients with normal coronary arteries in this single center cross-sectional study between November 2017 and March 2018 at Numune Education and Research Hospital, Ankara, Turkey. The study protocol was approved by the local ethical committee and informed consent forms were obtained from all participants.

STEMI diagnosis were made according to the third universal definition of myocardial infarction document.[9] All STEMI patients underwent primary percutaneous coronary intervention and received guided medical treatment according to contemporary scientific knowledge. Patients who underwent elective coronary angiography and were found to have normal coronary arteries were included in the study as the control group. All STEMI patients and patients with normal coronary arteries were consecutively recruited in the study. Acute coronary syndrome patients without a STEMI diagnosis were excluded from the study. Patients with any hematological disorder, chronic inflammatory disease, previous stroke, stable coronary artery disease, heart failure, renal disease, liver disease, malignancy, rheumatological disease, previous myocardial infarction or history of coronary artery surgery were also excluded. Transthoracic echocardiography was performed on all participants. Left ventricular ejection fraction was calculated using the Simpson's method.

Laboratory tests

All blood samples for serglycin analysis were collected from the patients after angiography, into plain tubes, and the serum was separated by centrifugation at 4000 rpm for 10 min and stored at −80 °C. Complete differential blood counts were determined in peripheral venous blood samples obtained upon admission. An automated analyzer was used to measure troponin, high-sensitivity C-reactive protein (hs-CRP), total cholesterol, triglyceride, creatinine and low- and high-density lipoprotein cholesterol levels. Serum serglycin levels were measured by a human serglycin enzyme-linked immunosorbent assay kit (Lot No.: E17-109S01, BioVendor Research and Diagnostic Products, 62100 Bmo, Czech Republic). All samples were processed simultaneously.[5] The coefficients of variation (CV) of the kit were 3.7% and 2.9% for 57.77 ng/mL and 81.57 ng/mL concentrations, respectively, and the sensitivity was 9.5 ng/mL.

Statistical analysis

The software package SPSS 22.0 was used to perform all statistical analyses. Distribution of the variables was analyzed using the Kolmogorov–Smirnov test. Continuous data were presented as means ± standard deviation or as medians with interquartile ranges, depending on the distribution pattern. Independent-samples t-test was used to compare parametric continuous variables and the Mann–Whitney U-test was used to compare nonparametric continuous variables. Categorical variables were compared using the chi-square test and expressed as percentages. The correlation between hs-CRP and serglycin levels was assessed by Spearman's rank test. For the multivariate analysis, the possible factors identified in univariate analysis were further entered into the logistic regression analysis to determine the independent predictors of myocardial infarction. The capacity of serum serglycin levels in predicting STEMI were analyzed using the ROC (receiver operating characteristic) curve analysis. While evaluating the area under curve, a 5% type-I error level was used to accept a statistically significant predictive value of the test variable. As there was no data about serglycin levels in coronary artery disease patients in the literature written in English, we were not able to calculate sample size before the study.

Results

A total of 132 patients (75 STEMI and 57 NCA) were included in the study. The clinical characteristics and biochemical parameters of the STEMI and control groups are presented in Table 1. Male patient ratio and smoking rate were higher in the STEMI group. Patients were younger in the control group than in the STEMI group. Serum serglycin levels were significantly higher in the STEMI group than in the control group (Table 1). Serum serglycin levels were significantly correlated with troponin ($r=0.419$, $p<0.001$) and hs-CRP ($r=0.336$, $p<0.001$; Figure 1 and 2) levels. Logistic regression analyses revealed that gender (male), fasting blood glucose level, hs CRP and serglycin levels were independent predictors of STEMI (Table 2). ROC analysis was performed to determine the serglycin level capability to predict STEMI. The area under the curve was 0.809 (95% confidence interval: 0.737–0.881; $p<0.001$). Using a cutoff level of 80.47 μg/L, the serglycin level predicted the presence of STEMI with a sensitivity of 75.7% and specificity of 68.4% (Figure 3).

Discussion

In this study, we found that serum serglycin levels were significantly increased in STEMI patients compared to control individuals. We showed that serglycin levels were positively correlated with troponin levels and CRP levels. To the best of our knowledge, this is the first study evaluating serum serglycin levels in STEMI patients and demonstrating a potential association between serglycin levels and prognostic markers in patients with STEMI.

Proteoglycans have some important functions in vascular bed, including extracellular matrix (ECM) formation and organization, regulation of cell-to-cell and cell-to-ECM interaction. Thus, proteoglycans functions in hemostasis adhesion, aggregation, migration, regulation and lipoprotein accumulation.[10] Serglycin is a proteoglycan which can be synthesized by immune cells and endothelial cells and it interacts with numerous mediators such as proteases, chemokines, cytokines and growth factors.[11] Previous preclinical studies showed some evidence about the potential role of serglycin in inflammation, atherogenesis and thrombosis.

Table 1 – Baseline characteristics and laboratory parameters of the study population

	CONTROL GROUP (*n*=57)	STEMI GROUP (*n*=75)	p
Male, *n (%)*	30 (52.6)	53 (71.6)	0.025
Age (years)	57 (51-64)	58 (52-70)	0.253
Diabetes, *n (%)*	13 (22.8)	25 (33.8)	0.170
Hypertension, *n (%)*	20 (35.1)	30 (40.5)	0.524
Smoking, *n (%)*	16 (28.1)	40 (66.7)	<0.001
Family history	1 (1.8)	6 (10)	0.115
LVEF (%)	64.9±0.4	45.58±10.3	<0.001
Fasting blood glucose, mg/dl	103 (94-125)	123 (98-155)	<0,001
Urea, mg/dl	31.5 (27-36)	38 (28-49)	0.095
Creatinine, mg/dl	0.83 (0.69-0.98)	1.05 (0.9-1.17)	0,001
Hemoglobin, g/dl	14.2±2.3	13.2±2.1	0.013
White blood cell count, 10/L	8 (6.8–9.6)	9.5 (8–12.3)	<0.001
Platelet count, 10/L	266±63.7	247.5±80.1	0.154
Total cholesterol, mg/dl	183.9±38.8	173.9±44.9	0.197
Triglycerides, mg/dl	143 (92–187)	127.5 (87.5–189.5)	0.221
HDL, mg/dl	45.6±13.7	43.2±12.8	0.329
LDL, mg/dl	107.2±36.5	101.3±36.3	0.371
hs-CRP, mg/L	3 (1–6)	12 (5–29)	<0.001
Serglycin, µg/L	57.13±32.2	102.81±39.42	<0.001
Troponin, ng/L	-	4175 (1700–8690)	NA

Data are presented as mean ± standard deviation, number and percentage (in brackets), or median and interquartile range 25–75. HDL: high density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, LDL: low density lipoprotein, STEMI: ST-segment elevation myocardial infarction

It was demonstrated that serglycin is expressed in all immune cells. Maturation of precursor immune cells, deposition and release of many important intracellular active molecules need serglycin.[12] Tumor necrosis factor, interleukin 1 beta and liposaccharide are important inflammatory mediators and these mediators upregulate serglycin synthesis.[13] It was demonstrated that serglycin deficient cells exhibit significantly decreased inflammatory marker production and nuclear factor kappa beta activation despite inflammatory stimulation.[14] This establishes that serglycin participates in the extension of inflammatory response. Platelets are also an important source of serglycin. It was previously demonstrated that serglycin is the dominant proteoglycan of the platelet alfa granules and serglycin deficiency results in aggregation defects and deteriorated platelet-derived inflammatory response.[7] Serglycin has an active role in endothelial functions. Serglycin expression and secretion was found to be higher in activated endothelial cells than in quiescent endothelial cells.[15]

Data derived from human studies about serglycin are meagre and limited; but these studies provide important evidence about a potential association between serglycin and atherosclerotic cardiovascular disease. In a recent study, serglycin was found to be among the most abundantly expressed proteins in adipocytes of epicardial adipose tissue in patients with CAD.[16] It was also demonstrated that the tumor necrosis factor-α (TNF-α) induces the expression and secretion of serglycin in adipocyte. In another study, serglycin was found to be associated with coronary artery ectasia, which is accepted as a variant of coronary atherosclerotic disease.[17] In addition, it was found that serum serglycin levels were correlated with Syntax score in patients with stable angina pectoris.[18]

Our results revealed confirmatory findings about the potential association of serglycin with inflammation and myocardial infarction. We determined that serum serglycin levels were higher in STEMI patients than in control individuals. Serum serglycin levels were positively correlated with peak troponin levels and hs CRP levels. It is not clear from our results whether serglycin elevation is a cause of myocardial infarction or it is a secondary finding due to inflammatory response or infarction. Although our results fail to give a clear explanation of the relationship between STEMI pathogenesis and serglycin, this study provides precious data about the association between serglycin levels with inflammation and infarction size.

Limitations of the study

The findings of our study should be interpreted with some caution due to the following limitations. This was a single-center, small-scale, cross sectional study. We did not collect any data about hard outcomes like death or symptomatic heart failure so we cannot make any comments about the association between serglycin levels and adverse cardiovascular events in STEMI

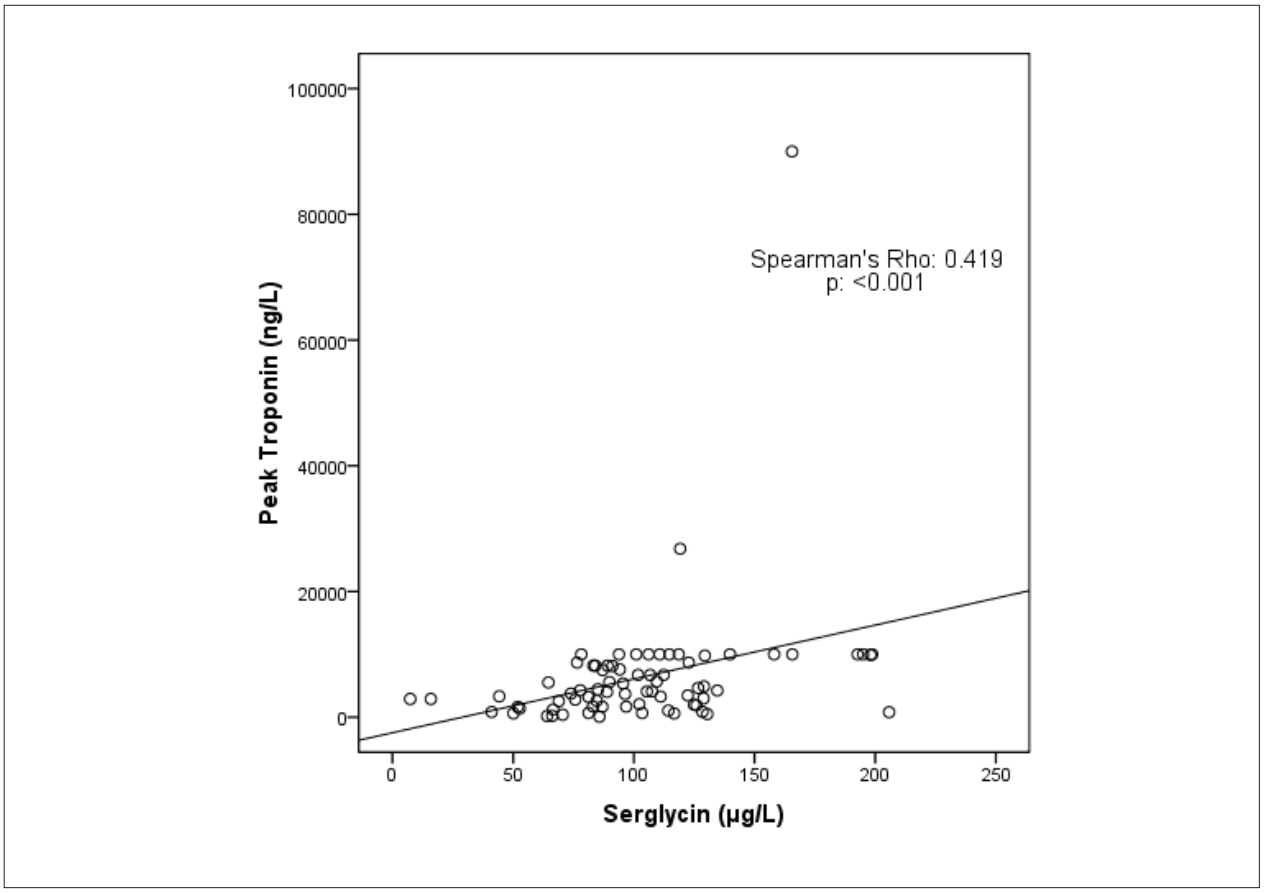


Figure 1 - *Correlations between plasma serglycin level and troponine level in STEMI patients. There was a significantly positive correlation between plasma serglycin level and troponine level in STEMI patients (r=0.419, p<0.001).*

patients. Besides, we did not gather any data reflecting the prognosis of STEMI like TIMI score, GRACE score, Killip class or BNP levels. But we believe that this study provides significant information by demonstrating the association of serglycin with hs CRP and peak troponin levels. We did not make serial serum serglycin measurements in STEMI patients. So, it is impossible to make any comments about how serglycin levels change in the course ofmyocardial infarction with this study.

Conclusions

This study has two major findings. One is the association between serglycin and inflammatory response demonstrated by hs CRP. The other is the association between serglycin and infarct size demonstrated by peak troponin levels. Our results may be a source of inspiration for studies evaluating the role of serglycin in acute coronary syndrome pathogenesis. We are of the opinion that further, more extensive studies are needed to further clarify the relationship between serglycin and STEMI.

Author Contributions

Conception and design of the research: Ilgın BU, Ornek E; Data acquisition: Ilgın BU, Gök M, Topcuoglu C, Çetin M, Karayiğit O; Analysis and interpretation of the data and Writing of the manuscript: Ilgın BU, Kızıltunç E; Statistical analysis: Kızıltunç E; Obtaining financing: Ilgın BU; Critical revision of the manuscript for intellectual content: Ilgın BU.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by Ankara Numune Education and Research Hospital.

Study Association

This article is part of the thesis of master submitted by Burcu Ugurlu Ilgın, from Ankara Numune Education and Research Hospital.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the Ankara Numune Education and Research Hospital under the protocol number E-17-1225 . 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.

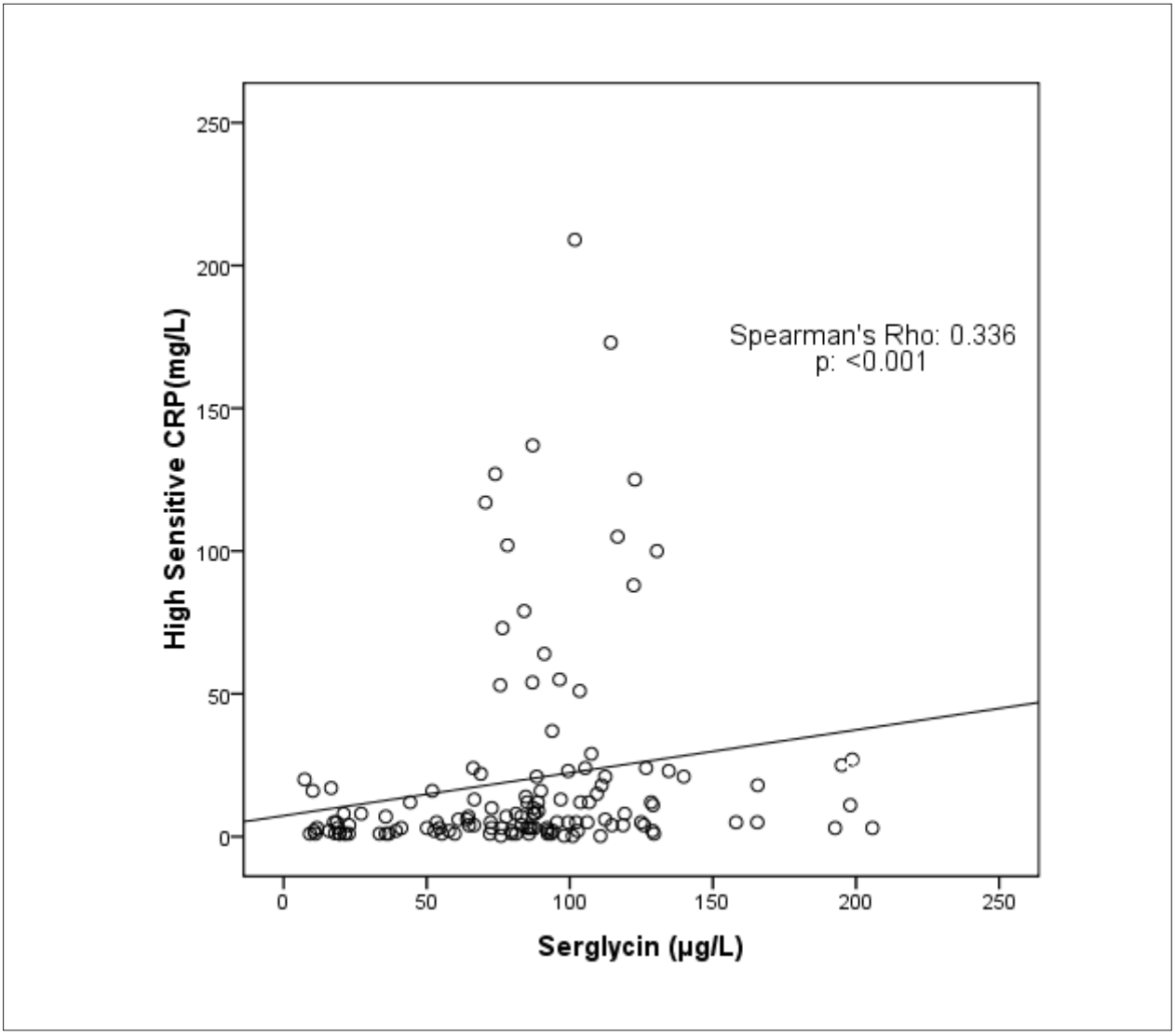


Figure 2 – *Correlations between plasma serglycin level and hs-CRP level in STEMI patients. There was a significantly positive correlation between plasma serglycin level and hs-CRP level in STEMI patients (r=0.336, p<0.001).*

Table 2 – Univariate and multivariate analysis showing the predictors of STEMI

Variable	Univariate		Multivariate	
	B (95% CI)	p	B (95% CI)	p
Male gender	2.27 (1.10–4.70)	0.027	21.92 (2.58–185.76)	0.005
Smoking	5,12 (2.32–11.28)	<0.001	2.72 (0.59–12.59)	0.199
Age	1.03 (0.98–1.05)	0.063	1.04 (0.98–1.11)	0.173
Fasting blood Glucose	1.01 (1.07–1.02)	0.001	1.02 (1,01–1,03)	0.007
Urea	1.03 (1.01–1.07)	0.024	1.03 (0.98–1.08)	0.229
Creatinine	0.97 (0.89–1.05)	0.468		
Hemoglobin	0.81 (0.68–0.96)	0.016	0.80 (0.60–1.06)	0.129
White blood cell	1.00 (0.99–1.01)	0.625		
hs CRP	1.14 (1.07–1.22)	<0.001	1.17 (1.03–1.33)	0.012
Serglycin	1.04 (1.02–1.05)	<0.001	1,01 (1,00–1,01)	0.006

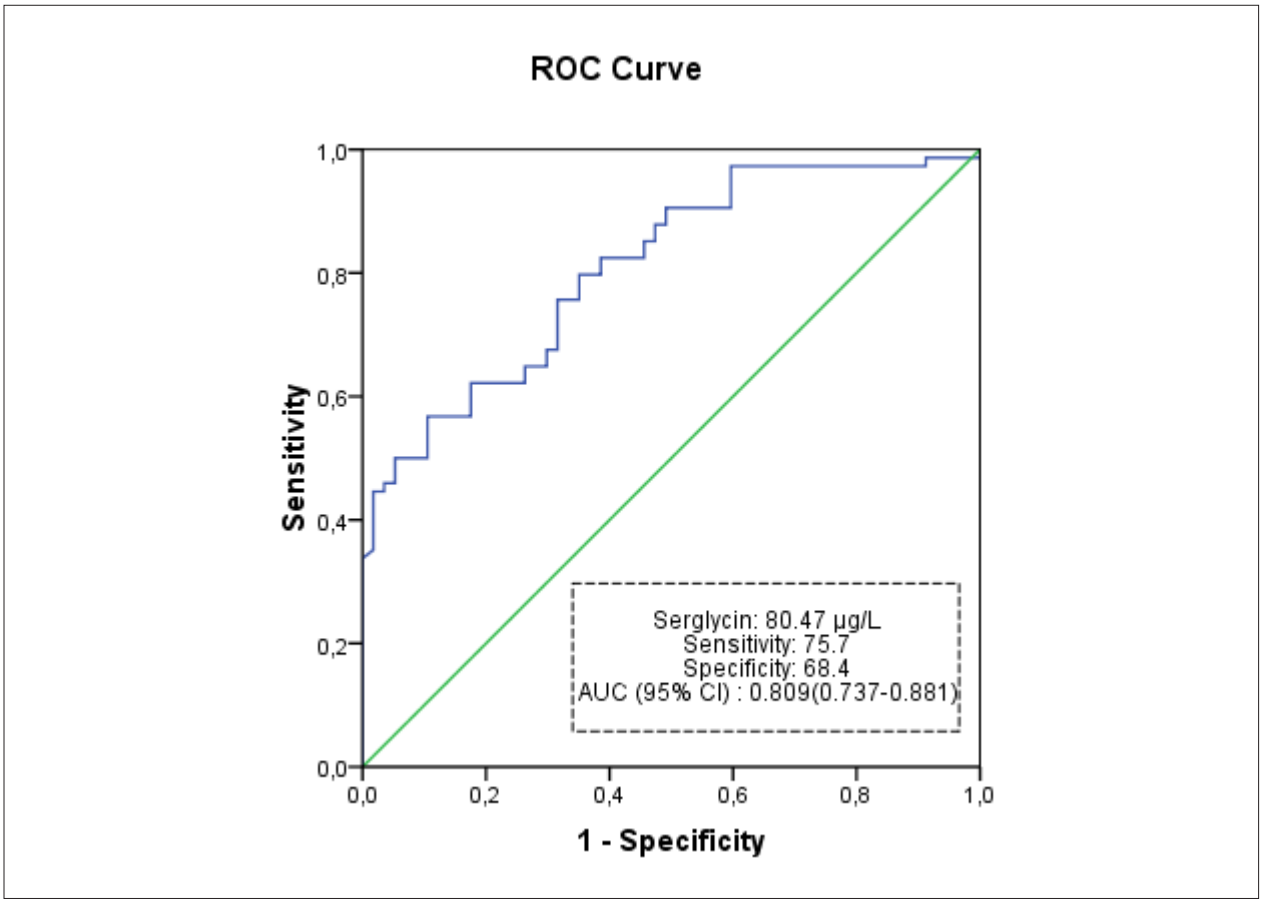


Figure 3 – *ROC analysis.*

References

1. Zakynthinos E, Pappa N. Inflammatory biomarkers in coronary artery disease. J Cardiol. 2009;53(3):317–33.
2. Hansson GK. Inflammation, Atherosclerosis, and Coronary Artery Disease. N Engl J Med [Internet]. 2005;352(16):1685–95. Available from: https://www.nejm.org/doi/full/10.1056/NEJMra043430
3. Kolset SO, Tveit H. Serglycin - Structure and biology. Cell Mol Life Sci. 2008;65(7–8):1073–85.
4. Zernichow L, Åbrink M, Hallgren J, Grujic M, Pejler G, Kolset SO. Serglycin is the major secreted proteoglycan in macrophages and has a role in the regulation of macrophage tumor necrosis factor-α secretion in response to lipopolysaccharide. J Biol Chem. 2006;281(37):26792–801.
5. Reine TM, Vuong TT, Jenssen TG, Kolset SO. Serglycin secretion is part of the inflammatory response in activated primary human endothelial cells in vitro. Biochim Biophys Acta - Gen Subj [Internet]. 2014;1840(8):2498–505. Available from: http://dx.doi.org/10.1016/j.bbagen.2014.02.002
6. Kolseth IBM, Reine TM, Vuong TT, Meen AJ, Fan Q, Jenssen TG, et al. Serglycin is part of the secretory repertoire of LPS-activated monocytes. Immunity, Inflamm Dis. 2015;
7. Woulfe DS, Lilliendahl JK, August S, Rauova L, Kowalska MA, Åbrink M, et al. Serglycin proteoglycan deletion induces defects in platelet aggregation and thrombus formation in mice. Blood. 2008;111(7):3458–67.
8. Schick BP. Serglycin Proteoglycan Deletion in Mouse Platelets : Physiological Effects and Their Implications for Platelet Contributions to Thrombosis , Inflammation , Atherosclerosis , and Metastasis I . Progr Mol Biol Trans Sci.2010;93:235-7.
9. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Alpert JS, White HD, et al. Third universal definition of myocardial infarction. Eur Heart J. 33(20): 2012;2551–67.
10. Chang MY, Chan CK, Braun KR, Green PS, Brien KDO, Chait A, et al. Monocyte-to-Macrophage Differentiation SYNTHESIS AND SECRETION OF A COMPLEX EXTRACELLULAR MATRIX *. 2012;287(17):14122–35.
11. Kolset SO, Pejler G. Serglycin: A Structural and Functional Chameleon with Wide Impact on Immune Cells. J Immunol [Internet]. 2011;187(10):4927–33. Available from: http://www.jimmunol.org/lookup/doi/10.4049/jimmunol.1100806
12. Scully OJ, Chua P, Harve KS, Bay B, Yip GW. Serglycin in Health and Diseases. Anat Rec{Hoboken).2012;295(9):1415-20.
13. Korpetinou A, Skandalis SS, Labropoulou VT, Smirlaki G, Noulas A, Karamanos NK, et al. Serglycin: At the Crossroad of Inflammation and Malignancy. Front Oncol [Internet]. 2014;3(January):1–12. Available from: http://journal.frontiersin.org/article/10.3389/fonc.2013.00327/abstract
14. Scuruchi M, Ascola AD, Avenoso A, G GM, S SC, Campo GM. Contributed equally to this work. Arch Biochem Biophys. 2019;

15. Reine TM, Vuong TT, Rutkovskiy A, Meen AJ, Vaage J. Serglycin in Quiescent and Proliferating Primary Endothelial Cells. 2015;1–28.

16. Imoto-Tsubakimoto H, Takahashi T, Ueyama T, Ogata T, Adachi A, Nakanishi N, et al. Serglycin is a novel adipocytokine highly expressed in epicardial adipose tissue. Biochem Biophys Res Commun [Internet]. 2013;432(1):105–10. Available from: http://dx.doi.org/10.1016/j.bbrc.2013.01.078

17. Kundi H, Gök M, Topçuoglu C, Ornek E. Związek stężenia serglicyny z izolowanym tętniakowatym poszerzeniem tętnic wieńcowych. Kardiol Pol [Internet]. 2017;75(10):990–6. Available from: https://ojs.kardiologiapolska.pl/kp/article/view/11101

18. Bolayir HA, Kivrak T, Gunes H, Bolayir A, Karaca I. The association between serum serglycin level and coronary artery disease severity in patients with stable angina pectoris. Kardiol Pol. 2018;76(4):783-96.

Original Article

Recent Trends in Cardiovascular Mortality in Rio de Janeiro State Health Regions and Capital

Maria Luiza Garcia Rosa,[1] Claudio Tinoco Mesquita,[2] Lucas Zanetti de Albuquerque,[1] Willian Douglas de Souza Silva,[3] Vinicius de Padua Vieira Alves,[1] Roger Freitas Ramirez Jordan,[1] Ricardo Cardoso de Matos,[1] Ana Luisa Guedes de França e Silva,[1] Erito Marques de Souza Filho[3,4]

Universidade Federal Fluminense - Departamento de Epidemiologia e Bioestatística,[1] Niterói, RJ - Brazil
Universidade Federal Fluminense Faculdade de Medicina - Departamento de Radiologia,[2] Niterói, RJ - Brazil
Universidade Federal Fluminense - Departamento de Medicina Clínica,[3] Niterói, RJ - Brazil
Universidade Federal Rural do Rio de Janeiro - Departamento de Tecnologias e Linguagens,[4] Nova Iguaçu, RJ – Brazil

Abstract

Background: **Cardiovascular disease (CVD) mortality, after several decades of decrease, has shown a tendency towards the stabilization in some countries, including Brazil and Rio de Janeiro state. This new tendency was not further analyzed by gender, age group and region of the Rio de Janeiro state.**

Objective: **To analyze the trends of premature and late mortality from CVD, ischemic heart disease (IHD) and cerebrovascular disease (CBVD) by gender in the city of Rio de Janeiro (capital) and the health regions of Rio de Janeiro state (from 1996 to 2016.**

Methods: **Data on deaths and the population were obtained from DATASUS/MS. The rates were compensated by ill-defined codes, corrected by Ill-Defined Cardiovascular codes and gender and age-adjusted by the direct method (reference population – population of the state of Rio de Janeiro - 2000 census). The Joinpoint Trend Analysis Software was employed.**

Results: **IHD mortality stabilized or even increased for at least 50% of the analyzed areas (EAPC≥0). No change was observed. in the "North" and "Northwest" regions For CBVD, just one region showed stability regarding mortality (EAPC close to 0). For the other regions, the rate continued to decrease (APC<0) until 2016.**

Conclusion: **These results observed in Rio de Janeiro are possibly appropriate to various Brazilian regions and demonstrate that a serious public health response is needed to address lifestyle behaviors. Primary care physicians should also be familiar with the unfavorable tendency in coronary heart disease among younger adults in recent years and actively screen for risk factors for cardiovascular disease, paying special attention to women. (Arq Bras Cardiol. 2021; 116(4):763-771)**

Keywords: **Cardiovascular Diseases/prevention and control; Cerebrovascular Diseases/prevention and control; Disease Prevention; Risk Factors; Life Style; Epidemiology**

Introduction

Cardiovascular diseases (CVDs) are a leading cause of premature death and chronic disability worldwide and a major obstacle to sustainable human development, with an estimated 422.7 million cases occurring worldwide in 2015 (424,058 of these cases in Brazil). In 2011, the United Nations formally recognized noncommunicable diseases, including CVDs, as a major concern for global health.

Mailing Address: Roger Freitas Ramirez Jordan •
Universidade Federal Fluminense - Epidemiologia e Bioestatística - Rua Buarque de Macedo. Postal Code 24033-900, Rio de Janeiro, RJ – Brazil
E-mail: rogerjordan6001@gmail.com
Manuscript received October 25, 2019, revised manuscript February 14, 2020, accepted March 16, 2020

DOI: https://doi.org/10.36660/abc.20190742

Sociodemographic changes over the past 25 years have been associated with dramatic declines in age-standardized rates of CVD mortality in regions with high sociodemographic Index (SDI), but only a gradual decrease in the rest of the globe despite impressive advances in technical capacity for preventing and treating CVD.[1-4] Data from the 2015 Global Burden of Disease (GBD) showed a reduction in age-related CVD mortality in Brazil and in Rio de Janeiro state between 1990 and 2015.[1-4]

In the last decade, international studies have observed a tendency towards the stabilization of these CVD mortality rates.[5-7] The same trend was observed in some Brazilian states, including in Rio de Janeiro.[4,8] However, this mortality rate stabilization in Rio de Janeiro state was not further analyzed by gender, age group nor between state regions and this decelerating decline in CVD mortality poses a new challenge for health policies at different levels of coverage. The objective

of this study is to analyze the trends of the premature and late mortality from CVD, ischemic heart disease (IHD) and cerebrovascular disease (CBVD) by gender, for the capital city and health regions of Rio de Janeiro state, between 1996 and 2016 to determine whether there have been any recent changes in the mortality decline pattern.

Methods

We obtained data on mortality and population for all individuals aged ≥20 years in the Rio de Janeiro state capital and health regions, between 1996 and 2016 from the DATASUS website.[8] According to the Brazilian Ministry of Health, a health region consists of a continuous geographical space consisting of groups of municipalities with defined limits, delimited based on cultural, economic and social identities and shared communication networks and transport infrastructure, with the intent of integrating organization, planning and implementation of health actions and services.[9]

Mortality was categorized as premature (30-69 years) and late (70 years or more) and was analyzed by gender and cause for the state capital city of Rio de Janeiro and regions of the state.[10] We considered all codes listed in chapter IX of ICD-10 for CVD and, specifically, the codes I20-I25 for IHD and I60-I69 for CBVD of ICD-10. The crude and gender- and age-adjusted mortality rates (by the direct method) were calculated per 100,000 individuals, for each locality. We assigned the deaths from ill-defined causes (IDC)– ICD codes RR00-RR99 – to the fractions observed in the defined deaths from CVD, IHD and CBVD (compensated deaths). The Ill-Defined Cardiovascular Codes – I46, I47, I48, I49, I50, I51 and I70 were assigned to the IHD cause, by gender and age category.[11] After those corrections, age-adjusted premature and late mortality rates were estimated, always for each cause, gender and locality. The reference population was the state of Rio de Janeiro population (2000 census), stratified into seven age groups (20 to 29 years; 30 to 39 years; 40 to 49 years old, 50 to 59 years old; 60 to 69 years old; 70 to 79 years old; and 80 years or older) in each gender. Those rates were denominated as compensated and adjusted.

Statistical Analysis

To evaluate the trends, the Joinpoint Trend Analysis Software version 4.7.0.0 was employed.[12] The Joinpoint Poisson regression model estimates the annual percentage change (APC) of crude and adjusted death rates. Then, the average annual percentage change (AAPC) is estimated as a weight average of the estimated APC using the period as the weight. Subsequently, it is tested whether the APC or AAPC are significantly different from zero using the unpaired Student's t-test, with alpha = 5%. The number of jointpoints was calculated by permutation test, using Bonferroni corrections, where the adjusted alpha level was 5%. The software assumes that the default value of the minimum number of jointpoints is 0. This method is the preferred one to produce more parsimonious results.

Results

We analyzed the regions of Rio de Janeiro state and the Rio de Janeiro city Capital from 1996 to 2016. During the entire period, the age-adjusted premature and late mortality rate for adults ≥20 years old plummeted to around 50% for all regions of the state of Rio de Janeiro and capital city in the three studied groups (CVD, IHD and CBVD), for both genders, when the AAPC ranged from -0.6% to -6.5%. In general, the premature mortality for men was higher than that for women for the three causes, which was not necessarily the same for late mortality. The late mortality coefficients were at least 10 times higher than those for premature mortality for both genders and for the three causes of mortality (Table 1).

From 1996 to 2016, for both genders, the premature IHD mortality stabilized or even reversed the trend for at least 50% of the analyzed areas (APC>0 or APC≅0%). The same happened for late IHD mortality for women. This change occurred in different moments between 2003 and 2014. In the "Metropolitan I region" the premature and late mortality from IHD for both men and women, has increased since 2008 or 2013. In the "North" and "Northwest" regions, no change was observed. In other regions and in Rio de Janeiro state capital, there was change in the tendency (APC>0 or APC≅0%) for some groups (Tables 2 and 3).

For CBVD, only one region showed stability in premature mortality (APC>0 or APC≅0%). For the other regions, either for premature or late mortality, for both men and women, the rate continued to increase until 2016 (Tables 2 and 3).

For the entire chapter IX (ICD X), CVD, we observed a change in the trend in premature mortality in four of the ten analyzed regions for men and in three regions for late mortality in women. The years during which these changes occurred went from 2001 to 2014. Metropolitan region 1 showed the largest number of changes in the mortality trend (Tables 2 and 3). In Rio de Janeiro city Capital, a decrease in mortality was observed for men regarding late mortality and for both genders regarding premature mortality. A decrease was observed for late mortality in women until 2011, followed by a reverse in rates, with a small increase until 2016. (Figure 1)

It is important to underscore that none of the cases which showed an increase in mortality had a statistically significant change.

Discussion

The present analysis aimed to identify changes in the trend of decreasing early and late cardiovascular mortality in the health regions of Rio de Janeiro state and city capital, between 1996 and 2016, according to gender.

At least 50% of the areas showed changes in IHD mortality, either stabilizing or increasing the rate, mostly due to premature mortality in men and for both types of mortality for women. The results were similar for CVD. These results are particularly challenging as premature mortality has a high social impact and confirms the evidence that there is a lack of identification of IHD, as well as undertreatment and undertesting of women as causes of higher mortality rates and increased morbid complications in the female gender.[13]

Table 1 – Premature and Late Adjusted Mortality coefficients of Cardiovascular Diseases (1996 – 2016) and respectives annual average percentual change (AAPC). Regions of Health of Rio de Janeiro State

Regions of Health of Rio de Janeiro State	Premature Mortality																	
	Men									Women								
	IHD			CBVD			CVD			IHD			CBVD			CVD		
	1996	2016	AAPC	1996	2016	AAPC	1996	2016	AAPC	1996	2016	AAPC	1996	2016	AAPC	1996	2016	AAPC
Rio de Janeiro City	139.24	90.57	-3,0*	82.39	33.76	-5,0*	115.21	67.00	-3,0*	68.00	43.46	-2,8*	59.31	25.33	-4,7*	59.73	35.49	-3,1*
"Baia de Ilha Grande"	147.07	62.91	-3,2*	105.65	31.04	-5,7*	109.68	46.83	-3,2*	62.72	34.61	-3,5*	69.98	44.44	-5,8*	43.72	27.39	-4,6*
"Baixada Litoranea"	155.30	103.73	-1,3*	86.82	25.67	-5,0*	109.84	86.96	-1,3*	83.22	43.07	-3,3*	93.35	30.13	-5,8*	61.51	30.78	-3,8*
"Centro Sul"	257.73	114.03	-3,5*	107.76	34.42	-5,3*	195.31	91.95	-3,5*	98.13	58.19	-3,2*	74.63	43.82	-4,8*	61.88	42.47	-2,3*
"Medio Paraiba"	168.61	105.69	-1,9*	105.83	39.62	-5,2*	122.03	86.27	-1,9*	88.17	48.73	-3,2*	87.73	39.23	-5,0*	58.13	37.83	-3,0*
"Metropolitana 1"	168.86	114.95	-1,5*	124.97	46.78	-4,9*	110.52	84.15	-1,5*	117.10	61.11	-3,0*	129.88	43.76	-5,9*	70.25	45.05	-2,1*
"Metropolitana 2"	136.54	96.13	-1,2*	93.03	37.91	-5,1*	100.95	80.30	-1,2*	77.24	45.91	-2,0*	80.04	32.95	-5,0*	52.80	36.39	-1,5*
"Noroeste"	131.49	77.97	-3,1*	125.75	37.59	-5,6*	96.52	57.22	-3,1*	87.25	35.31	-4,0*	53.99	37.14	-4,1*	64.01	28.35	-3,7*
"Norte"	106.09	80.96	-1,7*	123.00	44.90	-5,1*	71.51	67.02	-1,7*	48.09	42.89	-2,2*	119.25	34.02	-6,0*	30.35	32.48	-1,4*
"Serrana"	152.97	87.69	-2,6*	105.30	40.81	-4,1*	114.84	69.91	-2,6*	89.91	45.62	-3,5*	90.44	28.63	-4,9*	62.61	35.97	-3,3*

Regions of Health of Rio de Janeiro State	Late Mortality																	
	Men									Women								
	IHD			CBVD			CVD			IHD			CBVD			CVD		
	1996	2016	AAPC	1996	2016	AAPC	1996	2016	AAPC	1996	2016	AAPC	1996	2016	AAPC	1996	2016	AAPC
Rio de Janeiro City	1923.61	1082.27	-3,3*	1049.73	521.16	-3,9*	1380.79	785.98	-3,6*	1610.24	807.19	-3,3*	1517.42	733.19	-4,1*	1665.42	838.86	-3,5*
"Baia de Ilha Grande"	2383.76	1131.36	-3,5*	2309.17	802.26	-6,5*	1544.07	757.86	-2,9*	1940.82	881.83	-3,1*	889.86	322.97	-3,5*	1471.98	590.97	-2,5*
"Baixada Litoranea"	2002.98	1182.20	-2,3*	1667.89	627.68	-3,8*	1193.66	855.53	-1,5*	2497.11	1302.14	-2,7*	742.25	331.48	-3,5*	1495.59	839.08	-1,4*
"Centro Sul"	2519.52	1084.25	-4,3*	1527.20	766.98	-3,3*	1549.67	803.94	-3,3*	4040.84	1738.04	-4,1*	717.34	340.08	-4,5*	2080.28	1186.57	-3,9*
"Medio Paraiba"	1806.91	1161.65	-2,9*	1541.60	645.67	-3,2*	1103.77	813.33	-2,8*	2655.35	1139.76	-3,9*	676.70	309.13	-3,5*	1485.79	673.55	-3,7*
"Metropolitana 1"	2120.96	1508.72	-2,1	1661.28	732.68	-4,2*	1122.92	972.22	-1,5	3147.12	1710.64	-2,9*	826.65	295.70	-4,7*	1585.96	1067.85	-2,4*
"Metropolitana 2"	1776.36	1257.04	-2,1*	1350.81	710.51	-4,2*	1075.85	1020.13	-1,1*	2565.82	1381.72	-2,7*	622.74	253.48	-4,3*	1378.43	1084.99	-0,6
"Noroeste"	1743.15	971.07	-3,1*	1405.05	713.78	-3,9*	918.39	733.91	-2,0*	2390.88	1114.98	-3,6*	633.83	235.45	-5,0*	1157.58	691.96	-3,3*
"Norte"	1585.85	832.78	-2,7*	1862.91	854.98	-4,4*	865.80	565.06	-1,7*	2245.17	902.24	-4,0*	821.34	313.52	-4,3*	951.75	606.23	-2,3*
"Serrana"	2163.82	1178.74	-3,2*	1241.50	761.31	-3,4*	1503.60	834.87	-2,9*	2753.49	1448.35	-3,5*	685.99	352.46	-3,5*	1465.26	970.06	-3,7*

*IHD: ischemic heart disease; CBVD: cerebrovascular disease; CVD: cardiovascular diseases; * Pvalue<0.05.*

Table 2 – Annual percent change (APC) in cardiovascular premature mortality for Rio de Janeiro capital and regions of Rio de Janeiro state. 1996-2016

Premature Mortality					
Disease group	Health region	Men		Women	
		Period	APC	Period	APC
	Rio de Janeiro City	1996-2003	-4,2*	1996-2000	-9,5*
		2003-2008	-0,8	2000-2016	-1,1*
		2008-2014	-3,4*		
		2014-2016	4,2		
	"Baia de Ilha Grande"			1996-2010	-7,7*
				2010-2016	7,2
	"Baixada Litoranea"			1996-1998	-24,8*
				1998-2004	3,4
				2004-2008	-6,9
				2008-2016	-0,3
IHD	"Centro Sul"	1996-2007	-6,8*		
		2007-2016	0,2		
	"Medio Paraiba"	1996-2010	-4,2*	1996-2010	-5,3*
		2010-2016	1,7	2010-2016	1,8
	"Metropolitana 1"	1996-2009	-3,7*	1996-2008	-5,5*
		2009-2016	2,0	2008-2016	0,8
	"Metropolitana 2"	1996-2009	-2,7*	1996-2009	-4,1*
		2009-2016	0,4	2009-2016	2,0
	"Noroeste"				
	"Norte"				
	"Serrana"				
	Rio de Janeiro City				
	"Baia de Ilha Grande"				
	"Baixada Litoranea"	1996-2005	-2,3		
		2005-2016	-7,2*		
	"Centro Sul"				
	"Medio Paraiba"				
CBVD	"Metropolitana 1"	1996-2013	-5,5*		
		2013-2016	-1,8		
	"Metropolitana 2"				
	"Noroeste"				
	"Norte"				
	"Serrana"	1996-2009	-6,3*		
		2009-2016	-0		

Continuation

CVD	Rio de Janeiro City	1996-2003	-4,7*	1996-2000	-8,9*
		2003-2008	-1,2	2000-2016	-1,6*
		2008-2014	-5,1*		
		2014-2016	5,8		
	"Baia de Ilha Grande"				
	"Baixada Litoranea"			1996-1998	-27,3*
				1998-2003	4.6
				2003-2016	-2,7*
	"Centro Sul"	1996-2005	-7,5*		
		2005-2016	-0		
	"Medio Paraiba"	1996-2012	-3,6*	1996-2010	-5,0*
		2012-2016	5,2	2010-2016	1.7
	"Metropolitana 1"	1996-2006	-3,0*	1996-2008	-3,7*
		2006-2016	0	2008-2016	0,5
	"Metropolitana 2"			1996-2007	-3,6*
				2007-2016	1,2
	"Noroeste"				
	"Norte"				
	"Serrana"				
	"Serrana"				

*APC: annual percent change; IHD: ischemic heart disease; CBVD: cerebrovascular disease; CVD: cardiovascular diseases; * Pvalue<0.05.*

In a global scale, the average age-standardized CVD death rate continuously followed a pattern of reduction in the decades of 1990s and 2000s, with the greatest decline occurring between 2000 and 2005. This mostly counted on the reduction of mortality rates due to IHD and CBVD, with the latter also showing the most prominent percentage reductions in premature and late death coefficients in all Rio de Janeiro health regions and capital city.[14] Also, low and middle-income regions around the world have shown a decrease of 13% in age-standardized rates of death attributable to CVD but with a significant 66% growth in the number of deaths between 1990 and 2013.[14] Despite that, this increase in CVD deaths due to population growth and aging was compensated by a reduction in age-specific death rates in Brazil, indicating possible improvements in the population's health quality.[15] However, the global distribution of CVD is a complex one, influenced by national and regional characteristics, which results in significant differences between and within regions, making comparisons difficult to accomplish.

In the USA, the rate of decline in all cardiovascular diseases substantially decelerated after 2011.[5] It is argued that, in part, the decline is due to the increasing prevalence of obesity and diabetes at epidemic proportions in recent years, overcoming the benefits of prevention policies, the effects of primary prevention and advances in the treatment of hypertension, diabetes and dyslipidemia.[1,3,16] In Brazil, although the coverage of the national mortality surveillance system has been expanded and the quality of death certification has improved, with a higher proportion of correct diagnoses,[17] the same is not observed for the evaluation of risk factor prevalence. The only source of serial cardiovascular risk factors in Brazil is the "Vigitel", which covers only the state capitals. This national and annual phone survey is criticized by some for being self-reported. Based on data collection carried out in 2006 and 2016, we observed that there was an increase in self-reported hypertension and obesity for Rio de Janeiro state capital , whereas there was a decrease in self-reported smoking status.[18]

Other review studies, such as the one performed by Picon et al., has estimated prevalence rates for hypertension in Brazil of 28.7% (95% confidence interval [CI], 26.2–31.4), for both genders in all federation units.[19] A considerable number of other studies about the prevalence of CVD risk factors in our country can be found in the literature, but most have methodological limitations related to spatial coverage or absence of confirmatory laboratory examinations. [20]

In all Rio de Janeiro regions, the changes in IHD or CVD mortality trends, with stabilization or even increase of the rates, were observed between 2004 and 2014. In fact, evidence

Table 3 – Annual percent change (APC) in cardiovascular late mortality for Rio de Janeiro capital and regions of Rio de Janeiro state. 1996-2016

Late mortality					
Disease group	Health region	Men		Women	
		Period	APC	Period	APC
IHD	Rio de Janeiro City			1996-2011	-5,4*
				2011-2016	3,3
	"Baia de Ilha Grande"				
	"Baixada Litoranea"				
	"Centro Sul"			1996-2010	-6,7*
				2010-2016	2,2
	"Medio Paraiba"				
	"Metropolitana 1"	1996-2001	-7,8*	1996-2008	-6,0*
		2001-2013	-1,9*	2008-2016	1,9
		2013-2016	7,6		
	"Metropolitana 2"			1996-2010	-5,4*
				2010-2016	3,7
	"Noroeste"				
	"Norte"				
	"Serrana"			1996-2005	-3,1*
				2005-2009	-9,3
				2009-2016	-0,7
CBVD	Rio de Janeiro City	1996-2004	-1,8*		
		2004-2016	-5,2*		
	"Baia de Ilha Grande"	1996-1998	-43,4*		
		1998-2016	-1,1		
	"Baixada Litoranea"				
	"Centro Sul"				
	"Medio Paraiba"				
	"Metropolitana 1"				
	"Metropolitana 2"				
	"Noroeste"				
	"Norte"				
	"Serrana"				
CVD	Rio de Janeiro City			1996-2012	-5,1*
				2012-2016	2.9
	"Baia de Ilha Grande"				
	"Baixada Litoranea"				
	"Centro Sul"				
	"Medio Paraiba"				
	"Metropolitana 1"	1996-2001	-6,2*	1996-2001	-7,8*
		2001-2016	0,1	2001-2016	-0,5
	"Metropolitana 2"			1996-2006	-2,2*
				2006-2009	-10,4
				2009-2016	6,3*
	"Noroeste"			1996-2012	-1,2
				2012-2016	-11,2*
	"Norte"				
	"Serrana"				
	"Serrana"				

APC: annual percent change; IHD: ischemic heart disease; CBVD: cerebrovascular disease; CVD: cardiovascular diseases; Pvalue<0.05.*

that cardiovascular mortality rates for young adults in the USA could be stabilizing or even showing early nonsignificant signs of an increase was first published in 2007.[21] Many factors can be related to this observed regional trend, and data showing health and quality of life improvements makes it harder to understand the reason this flattening trend was observed. Supplementary health coverage in the state of Rio de Janeiro in 2013 was 33.5%, with an annual increase of 0.78% between 2004 and 2013. Inverse linear correlations with mortality rates due to CVD and CBVD were observed, which must be questioned due to possibility of other facts, since the simultaneous increase in municipal human development index in all federal units between 2000 and 2010 can also have affected these rates.[21]

As discussed by Soares et al. in two different articles, socioeconomic improvements preceded the decline in mortality due to cardiovascular diseases.[23,24] The reduction in the mortality rates, particularly from IHD in the Rio de Janeiro state in the past decades, was preceded by an increase in the Human Development Index (HDI).[23] Only a few municipalities in the Rio de Janeiro state showed a decrease in the HDI between 1970 and 1991. Some of them are located in the "north" and "northwest" regions, where the mortality from IHD is continuously declining. These observations allow us to raise the hypothesis that these municipalities are benefiting from socioeconomic improvements that occurred earlier in the regions where there was an inversion in the mortality trend, drawing attention to the "Metropolitan I" region.

In the USA, the decline in all CVD mortality has decelerated substantially, including CBVD, which did not occur in Rio de Janeiro health regions and capital city.[2] This may be explained by the delay in the implementation of primary prevention measures for ischemic stroke (statins, aspirin, antithrombotic therapy) compared to developed countries. At the national scale, the flattening pattern of mortality rate due to CVD observed in recent years serve as a warning signal to the need for continuing monitoring of trends and the possibility of emergence of significant countertrends.[2] The public health network, with programs such as Family Health Strategy and Popular Pharmacy Program, are undoubtedly important in controlling hypertension and other cardiovascular risk factors.[25,26] Effective national anti-tobacco and obesity prevention campaigns and national control plans and other policies with the objective to monitor and reduce risk factors were part of the recent history of Brazil national public health system development.[27-298] Understanding the mechanisms that may be hindering its effectiveness is a crucial step.

Limitations

The present study has some limitations. One of them is the quality of death certificates, which is different for the municipalities that comprise the regions, and varied over time, affecting the observed trends. The second limitation is the existence of municipalities with small populations that comprise the regions, which leads to large oscillations in the occurrence of infrequent events, such as death. The third limitation is the lack of information about the prevalence of cardiovascular risk factors for the analyzed areas.

Conclusion

The adverse IHD and CVD mortality trends observed in young adult men and in young and older women were observed in 50% of the Rio de Janeiro regions. These results are possibly appropriate to several regions of the country and demonstrates that a serious public health response is needed to address lifestyle behaviors. Primary care physicians should also be familiar with the unfavorable tendency in coronary heart disease in younger adults in recent years and actively screen for risk factors for cardiovascular disease, paying special attention to women.

Author Contributions

Conception and design of the research: Rosa MLG, Mesquita CT, Albuquerque LZ, Silva WDS, Alves VPV, Matos RC, Souza Filho EM; Acquisition of data, Statistical analysis and Writing of the manuscript: Rosa MLG, Mesquita CT, Albuquerque LZ, Silva WDS, Alves VPV, Jordan RFR, Matos RC, Silva ALGF, Souza Filho EM; Analysis and interpretation of the data: Rosa MLG, Mesquita CT, Albuquerque LZ, Matos RC, Souza Filho EM; Obtaining financing: Albuquerque LZ; Critical revision of the manuscript for intellectual content: Rosa MLG, Mesquita CT, Albuquerque LZ, Silva WDS, Alves VPV, Jordan RFR, Souza Filho EM.

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.

Sources of Funding

There was no external funding source for this study.

Study Association

This study is not associated with any thesis or dissertation.

Ethics Approval and Consent to Participate

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

References

1. Sidney S, Quesenberry CP Jr, Jaffe MG,Sorel M, Huynh M, Kusbi L, et al. Recent trends in cardiovascular mortality in the United States and public health goals. JAMA Cardiol. 2016;1(5):594-9.
2. Nowbar AN, Gitto M, Howard JP,Francis DP, Lamee RA. Mortality from ischemic heart disease. Circ Cardiovasc Qual Outcomes. 2019;12(6):e005375.
3. O'Flaherty M, Allender S, Taylor R,Stevenson C, Peeters A, Capewell S. The decline in coronary heart disease mortality is slowing in young adults (Australia 1976–2006): a time trend analysis. Int J Cardiol. 2012;158(2):193-8.
4. Brant LCC, Nascimento BR, Passos VMA, Duncan BB, Bensenor IJM, Malta DC, et al. Variations and particularities in cardiovascular disease mortality in Brazil and Brazilian states in 1990 and 2015: estimates from the Global Burden of Disease. Rev Bras Epidemiol. 2017;20(Suppl 1):116-28.
5. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, regional, and national burden of cardiovascular diseases for 10 causes, 1990 to 2015. J Am Coll Cardiol. 2017;70(11):1-25.
6. Lotufo PA. The pace of reduction of cardiovascular mortality in Brazil (1990 to 2017) is slowing down. Sao Paulo Med J. 2019;137(1):3-5.
7. Brant LCC, Nascimento BR, Passos VMA,.Duncan BB, Bensenor IJM, Malta D, et al. Variations and particularities in cardiovascular disease mortality in Brazil and Brazilian states in 1990 and 2015: estimates from the Global Burden of Disease. Rev Bras Epidemiol. 2017;20(Suppl 1):116-28.
8. Brasil. Ministério da Saúde. DATASUS. Informações de Saúde. Estatísticas Vitais. [Acesso em agosto de 2019]. Disponível em:http://datasus.saude.gov.br/
9. Brasil. Ministério da Saúde Comissão Intergestores Tripartite. Resolução nº 1, de 29 de setembro de 2011. [Acesso em 14/02/2020]. Na rede mundial de computadores: Disponível em:http://bvsms.saude.gov.br/bvs/saudelegis/cit/2011/res0001_29_09_2011.html.
10. World Health Organization. (WHO). WHO Global NCD Action Plan 2013-2020 [Internet]. Genebra: World Health Organization, 2013 [acessado em 12 out. 2019]. Disponível em: https://www.who.int/nmh/events/ncd_action_plan/en/.
11. Soares DA, Gonçalves MJ. Mortalidade cardiovascular e impacto de técnicas corretivas de subnotificações e óbitos mal definidos. Rev Panam Salud Publica. 2012;32(3):199-206.
12. National Institute of Health. National Cancer Institute. Joinpoint Trend Analysis Software.[Citado em 12 out 2019]. Disponível em: https://surveillance.cancer.gov/joinpoint/
13. Rosen SE, Henry S, Bond R,Pearte T, Mieres JH. Sex-specific disparities in risk factors for coronary heart disease. Curr Atheroscler Rep. 2015; 17(8):49.
14. Roth GA, Huffman MD, Moran AE,Feigin V, Mensah GA, Naghavi M, et al. Global and regional patterns in cardiovascular mortality from 1990 to 2013. Circulation. 2015;132(17):1667-78.
15. Roth GA, Forouzanfar MH, Moran AE,Barber R, Nguyen G, Feigin VL, et al. Demographic and epidemiologic drivers of global cardiovascular mortality. N Engl J Med. 2015; 372(14):1333-41.
16. Wilmot KA, O'Flaherty M, Capewell S, Ford ES, Vaccarino V. Coronary heart disease mortality declines in the United States from 1979 through 2011: evidence for stagnation in young adults, especially women. Circulation. 2015; 132:997-1002.
17. França EB, Passos VMA, Malta DC,Abreu D, Vasconcelos AM, Carneiro M, et al. Cause-specific mortality for 249 causes in Brazil and states during 1990-2015: a systematic analysis for the global burden of disease study 2015. Popul Health Metr. 2017;15(1):39.
18. Vigitel Brasil 2016: vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico: estimativas sobre frequência e distribuição sociodemográfica de fatores de risco e proteção para doenças crônicas nas capitais dos 26 estados brasileiros e no Distrito Federal em 2016. Brasília, 2017.
19. Picon RV, Fuchs FD, Moreira LB,Riegel G, Fuchs SC. Trends in prevalence of hypertension in Brazil: a systematic review with meta-analysis. PLoS One. 2012; 7(10):e48255.
20. Ribeiro AL, Duncan BB, Brant LC,Lotufo P, Barreto SM. Cardiovascular health in Brazil: trends and perspectives. Circulation. 2016; 133(4):422-33.
21. Ford ES, Capewell S. Coronary heart disease mortality among young adults in the U.S. from 1980 through 2002: concealed leveling of mortality rates. J Am Coll Cardiol. 2007;50(22):2128-32.
22. Lotufo PA. The pace of reduction of cardiovascular mortality in Brazil (1990 to 2017) is slowing down. São Paulo Med J. 2019;137(1):3-5.
22. Villela PB, Klein CH, de Oliveira GMM. Socioeconomic factors and mortality due to cerebrovascular and hypertensive disease in Brazil. Rev Port Cardiol. 2019; 38(3):205-12.
23. Soares GP, Klein CH, Silva NA Progression of mortality due to diseases of the circulatory system and human development index in Rio de Janeiro Municipalities. Arq Bras Cardiol. 2016 Oct; 107(4):314-22.
24. Soares GP, Brum JD, Oliveira GM, Oliveira GMM, Klein CH, Silva NAS. All-cause and cardiovascular diseases mortality in three Brazilian states, 1980 to 2006. Rev Panam Salud Publica. 2010; 28(4):258-66.
25. Ceccon RF, Borges DO, Paes LG,Klafke JZ, Viecili PRN. Mortality due to circulatory disorders and the evolution of family health in Brazil: an ecological study. Cien Saude Colet. 2013;18(5):1411-6.
26. Santos-Pinto Cdu B, Costa Ndo R, Osorio-de-Castro CG. The "Farmácia Popular do Brasil" Program and aspects of public provision of medicines in Brazil. Cien Saude Colet. 2011;16(6):2963-73.
27. Levy D, de Almeida LM, Szklo A. The Brazil SimSmoke policy simulation model: the effect of strong tobacco control policies on smoking prevalence and smoking-attributable deaths in a middle income nation. PLoS Med. 2012; 9(11):e1001336.
28. Jaime PC, da Silva AC, Gentil PC, Claro RM, Monteiro CA. Brazilian obesity prevention and control initiatives. Obes Rev. 2013;14(Suppl 2):88-95.
29. Paim J, Travassos C, Almeida C,Macinko BL. The Brazilian health system: history, advances, and challenges. Lancet. 2011;377(9779):1778-97.

Current Cardiovascular Disease Death Rate in Rio De Janeiro State: More than Only a Dream in Rio

Antonio de Padua Mansur[1]

Instituto do Coração (InCor), Faculdade de Medicina, Universidade de São Paulo,[1] *São Paulo, SP - Brazil*

Short editorial related to the article: Recent Trends in Cardiovascular Mortality in Rio de Janeiro State Health Regions and Capital

Cardiovascular diseases (CVD) are the main causes of death in women and men in Brazil. Since 1980, there has been a significant reduction in mortality from these diseases. From 1980 to 2012, the smallest reduction was 31% for ischemic heart diseases (IHD) in men, and the largest reduction was 54% for cerebrovascular diseases (CBVD) in women.[1] Despite an important reduction in mortality due to IHD, the reduction in mortality due to CBVD was the one that most contributed to the total reduction in mortality due to CVD. However, comparative analyses of the periods from 1980 to 2006 with those from 2007 to 2012 showed a greater percentage reduction in mortality from CVD, IHD, and CBVD in the period from 1980 to 2006. In the period from 2007 to 2012, there was a significant, but less intense, reduction in mortality from CVD and CBVD when compared to the previous period, while mortality from IHD remained unchanged in women and men. The same phenomenon was observed in the USA and in some European countries for this period, and this unfavorable trend has been associated with the increase in the incidence of obesity and diabetes mellitus and with the inadequate control of risk factors.[2-4] The control of the main risk factors for CVD reduces CVD mortality by at least 50%, and the highlight in this process is primary prevention by controlling the main risk factors, namely hypertension, smoking, diabetes, and dyslipidemia.[5,6]

Hypertension is the main risk factor in the genesis of CBVD, while the other risk factors also participate in the genesis of IHD, which leads to greater difficulty in preventing IHD, justifying the unfavorable tendency of IHD compared to CBVD. Currently, socioeconomic status (family income, employment, education, and environmental factors) is also considered an independent risk factor for CVD that is equivalent to traditional risk factors.[7] The influence of socioeconomic status is one of the main factors responsible for the highest mortality from CVD in the least favored populations.

A recent study showed a marked reduction in mortality from IHD and CBVD in the most developed regions of Brazil (Southeast and South), which was not observed in other regions of the country.[8] Nevertheless, even the Southeast and South regions have very heterogeneous microregions from the socioeconomic point of view and rather heterogeneous death rate data from CVD. A study by Rosa et al. showed this heterogeneity in CVD mortality in health regions of the state of Rio de Janeiro, including the capital city.[9] Health regions were defined as "continuous geographic space consisting of groups of bordering municipalities, delimited based on cultural identities, economic and social and communication networks and shared transport infrastructure.'' They reported, in at least 50% of regions, unfavorable trends in premature (30 to 69 years) and late (≥ 70 years) mortality from CVD in specific periods from 1996 to 2016. In general, the adjusted mortality coefficients for CVD, IHD, and CBVD had a significant reduction for all regions in women and in men, when zero junction points were used in the Joinpoint Regression Program[10] (Table 1). However, when the authors used one or more junction points, that is, they divided the total regression line corresponding to the entire period from 1996 to 2016 in two or more periods, they found specific periods where premature and late mortality from IHD and CBVD increased or remained stable. Almost all of these specific periods were from the last years analyzed, from the period from 1996 to 2016. The analysis of these specific periods showed that practically all health regions had unfavorable results in mortality from CVD, IHD, and CBVD, with the following exceptions: premature CVD mortality in women in the city of Rio de Janeiro, all CVD death in men in the Baixada Litorânea region, IHD in women in the city of Rio de Janeiro and the Baixada Litorânea region, and late mortality due to IHD in the Metropolitan 2 and Northwest regions. In the other regions, according to the data available in Table 2, unfavorable trends in CVD mortality were observed in practically the entire state of Rio de Janeiro. The authors did not evaluate the causes of these unfavorable results; they suggested the influence of socioeconomic aspects and the inadequate control of risk factors, which probably must have occurred. Nevertheless, some data on CVD mortality were missing for some health regions, particularly in relation to CBVD in women.

In summary, improvements in socioeconomic conditions and the intensification of primary prevention programs for CVD are essential to reverse these late trends of CVD mortality in the state of Rio de Janeiro.

Keywords

Cardiovascular Diseases/mortality; Myocardial Ischemia; Risk Factors; Hypertension; Dyslipidemia; Diabetes Mellitus; Socioeconomics Factors; Education.

Mailing Address: Antonio de Padua Mansur •
Universidade de São Paulo Instituto do Coração - Av. Dr. Enéas C. Aguiar, 44. Postal Code 05403-000, São Paulo, SP – Brazil
E-mail: apmansur@yahoo.com

DOI: https://doi.org/10.36660/abc.20210203

References

1. Mansur AP, Favarato D. Trends in Mortality Rate from Cardiovascular Disease in Brazil, 1980-2012. Arq Bras Cardiol. 2016;107(1):20-5.
2. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29-322. Erratum in: Circulation. 2015;131(24):e535.
3. Wilmot KA, O'Flaherty M, Capewell S, Ford ES, Vaccarino V. Coronary heart disease mortality declines in the United States from 1979 through 2011: evidence for stagnation in young adults, especially women. Circulation. 2015;132(11):997-1002.
4. Jardim TV, Sousa AL, Povoa TI, Barroso WK, Chinem B, Jardim L, Bernardes R, Coca A, Jardim PC. The natural history of cardiovascular risk factors in health professionals: 20-year follow-up. BMC Public Health. 2015;15:1111.
5. Ford ES, Ajani UA, Croft JB, Critchley JA, Labarthe DR, Kottke TE, Giles WH, Capewell S. Explaining the decrease in U.S. deaths from coronary disease, 1980-2000. N Engl J Med. 2007;356(23):2388-98.
6. Mansur AP. Prevenção primária das doenças cardiovasculares. São Paulo: Editora da Universidade de São Paulo; 2019. 288p.
7. Schultz WM et al. Socioeconomic status and cardiovascular outcomes. Challenges and interventions. Circulation 2018;137:2166.
8. Mansur AP, Favarato D. Mortality due to Cardiovascular Diseases in Women and Men in the Five Brazilian Regions, 1980-2012. Arq Bras Cardiol. 2016;107(2):137-46.
9. Rosa MLG, Mesquita CT, Albuquerque LZ, et al. Recent Trends in Cardiovascular Mortality in Rio de Janeiro State Health Regions and Capital. Arq Bras Cardiol.2021; 116(4):763-771.
10. National Cancer Institute Division of Cancer Control and Population Sciences. Joinpoint regression program, version 4.7.0.0.[Cited in February 26, 2019] Available from:https://surveillance.cancer.gov/joinpoint/.

Cardiovascular Risk Factors in Cardiology Specialists from the Brazilian Society of Cardiology

Maria Emília Figueiredo Teixeira,[1,2] Priscila Valverde de O. Vitorino,[3] Celso Amodeo,[4] Tânia Martinez,[5] Andréa Araujo Brandão,[6] Eduardo Costa Duarte Barbosa,[7] Audes Diógenes Magalhães Feitosa,[8] Paulo Cesar B. Veiga Jardim,[9] Ana Luiza Lima Souza,[1,2] Weimar Kunz Sebba Barroso,[1,2]

Universidade Federal de Goiás - Liga de Hipertensão Arterial,[1] Goiânia, GO – Brazil
Universidade Federal de Goiás - Programa de Pós-Graduação em Ciências da Saúde,[2] Goiânia, GO - Brazil
Pontifícia Universidade Católica de Goiás - Escola de Ciências Sociais e da Saúde,[3] Goiânia, Goiás - Brazil
Escola paulista de Medicina da Universidade Federal de São Paulo (Unifesp EPM),[4] São Paulo, SP - Brazil
Hospital do Coração (HCor) – Lipids,[5] São Paulo, SP - Brazil
Universidade do Estado do Rio de Janeiro (UERJ) – Cardiologia,[6] Rio de Janeiro, RJ - Brazil
Instituto de Cardiologia - Laboratório de Investigação Clínica (LIC),[7] Porto Alegre, RS - Brazil
Laboratório de Imunopatologia Keizo Asami - Universidade Federal de Pernambuco - Clínica Médica,[8] Recife, PE - Brazil
Universidade Federal de Goiás – Cardiologia,[9] Goiânia, GO – Brazil

Abstract

Background: **A major cause of death worldwide, cardiovascular diseases and their prevalence in cardiologists are little known.**

Objectives: **To describe life habits and cardiovascular risk factors (CVRF) and to investigate the prevalence of diagnosis, awareness, and control of these CVRF among cardiologists members affiliated to and specialists from the Brazilian Society of Cardiology.**

Methods: **National multicenter cross-sectional study to assess Brazilian cardiologists using a questionnaire on life habits, preexisting diseases, current medications, anthropometric measurements, blood pressure, and levels of glucose and lipids.**

Results: **A total of 555 cardiologists were evaluated, of which 67.9% were male, with a mean age of 47.2±11.7 years. Most were non-smoker (88.7%) and physically active (77.1%), consumed alcohol (78.2%), had normal weight circumference (51.7%), and were overweight (56.1%). The prevalence of systemic arterial hypertension (SAH), diabetes mellitus (DM), and dyslipidemia (DLP) were 32.4%, 5.9%, and 49.7%, respectively, of which only 57.2%, 45.5%, and 49.6%, respectively, were aware of the diseases.**

Conclusions: **The Brazilian cardiologists participating in the study had a high prevalence of SAH, DM and DLP, but only a half of participants were aware of these conditions and, among these, the rates of controlled disease were low for SAH and DLP, although cardiologists are professionals with great knowledge about these CVRF. These findings represent a warning sign for the approach of CVRF in Brazilian cardiologists and encourage the conduction of future studies. (Arq Bras Cardiol. 2021; 116(4):774-781)**

Keywords: **Cardiovascular Diseases; Cardiologists; Risk Factors; Antropometry; Hypertension; Dsylipidemias; Diabetes Mellitus; Life Style.**

Introduction

Among cardiovascular risk factors (CVRF), systemic arterial hypertension (SAH), diabetes mellitus (DM), dyslipidemias (DLP), and smoking are the ones with the greatest impact on increased morbidity and mortality rates.[1] Furthermore, unfavorable life habits lead to overweight and, when combined, interfere significantly with the prevalence of CVRF,[2] with a consequent increase in the incidence of cardiovascular outcomes, such as sudden death, stroke, acute myocardial infarction (AMI), heart failure, peripheral artery disease, and chronic kidney disease.[3-5]

Health care professionals, including physicians, especially cardiologists, play a crucial role in diagnosing and treating cardiovascular diseases.[6] Additionally, Brazilian cardiologists are often perceived as the responsible for the overall health care of adult patients.[7] Therefore, cardiologists are expected, in addition to providing care, to serve as a role model and, particularly, to personally engage in healthy life habits.[8]

There are few studies assessing cardiovascular risk and life habits of Brazilian cardiologists;[9] thus, this study aimed to: (1) investigate life habits and CVRF and (2) identify the

Mailing Address: Weimar Kunz Sebba Barroso •
Universidade Federal de Goiás - Liga de Hipertensão Arterial – Av. Universitária Hospital das Clinicas. Postal Code 74605-220, Goiânia, GO – Brazil
E-mail: sebbabarroso@gmail.com
Manuscript received February 20, 2020, revised manuscript August 28, 2020, accepted 09, 2020

DOI: https://doi.org/10.36660/abc.20200125

prevalence of diagnosed, self-reported, and controlled SAH, DM, and DLP in cardiologists affiliated to and specialists from the Brazilian Society of Cardiology (Sociedade Brasileira de Cardiologia, SBC).

Methods

Type of study, population, sample, and inclusion criteria

National, descriptive, cross-sectional, multicenter study.

In 2017, Brazil had 451,777 physicians, with approximately 25,000 (5.5%) cardiologists;[1]; of these, 11,495 had a cardiology specialist degree (CSD).[11] The reference population consisted of 14,201 cardiologists members of the SBC from across the country in 2017, with state societies in 24 federative units. The research was conducted with cardiologists having CSD/SBC in an attempt to standardize the sample with regard to level of scientific knowledge.

The sample was selected by convenience and included 555 physicians with CSD/SBC and active members of SBC, which accounts for 4.8% of the reference population.

Sites of study execution and coordination

All 24 regional representatives of SBC/Board of Cardiovascular Health Prevention (FUNCOR) were invited to participate in the group of researchers working in this project. Of these, 15 accepted the invitation and, together with three other invited centers [Instituto Dante Pazzanese de Cardiologia (IDPC), Liga de Hipertensão Arterial da Universidade Federal de Goiás (LHA/UFG), and Unidade de Hipertensão da Universidade Estadual do Rio de Janeiro], totaled 18 research centers that were effectively included in the group of investigators and coinvestigators who collected data from May to October 2017.

Data collection was conducted in the following states: Bahia, Distrito Federal, Goiás, Mato Grosso, Mato Grosso do Sul, Minas Gerais, Pará, Paraíba, Paraná, Pernambuco, Rio de Janeiro, Rio Grande do Norte, Rio Grande do Sul, Rondônia, São Paulo, and Tocantins.

The entire work was coordinated by the Board of SBC/FUNCOR, together with the university institutions IDPC and LHA/UFG.

Study procedures

In-person meetings with all investigators were conducted in May and June 2017 to discuss study design and data collection. After receiving training, each investigator trained his/her local team for strict compliance with study procedures. Collectionwas made by the very responsible researcher physician, or by other dully trained cardiologists or medical students.

Study participants were explained about the aim of the study, the data collection method, and the informed consent form (ICF), which was read and signed by all participants before the start of any study procedure.

Interviews were conducted individually in a private room at a time and place previously agreed with the participants. The interview form contained questions on personal information, life habits, and personal disease history. Moreover, anthropometric blood pressure (BP) measurements were obtained, and glucose and lipid profile tests were performed.

Age was calculated from date of birth. Sex was categorized into male and female. The life habits assessed were smoking (yes/no); consumption of alcoholic beverages (yes/no, for any amount of consumption), and physical activity practice (yes/no and weekly physical activity time, with active individuals being those who reported at least 150 minutes of physical activity per week).[12]

Anthropometric variables collected were height, weight, and waist circumference. Height was reported by participants;[13] weight was measured using an OMRON HN-290T digital weight scale, without accessories and shoes and using light clothes.[14]

Body mass index (BMI) was calculated using the weight/height^2 formula[15] and classified into: underweight (< 18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2); overweight (25-29.9 kg/m^2); class 1 obesity (30-34.9 kg/m^2), class 2 obesity (35 -39.9 kg/m^2), and class 3 obesity (≥ 40 kg/m^2).[16]

Waist circumference was measured with an inelastic measuring tape[14] and considered high if greater than 88 cm for women and greater than 102 cm for men.[17]

BP was measured using an OMRON sphygmomanometer, model HBP 1100,[18-20] as recommended by 7th Brazilian Guidelines on Arterial Hypertension.[21] Three BP measurements were obtained, the first measurement was excluded, and the mean of the two subsequent measurements was calculated. Based on their mean BP values, participants were classified into those with normal BP (BP ≤ 120/80 mmHg), pre-hypertension (121-139/81-89 mmHg), or stage 1 hypertension (140-159/90-99 mmHg), stage 2 hypertension (160-179/100-109 mmHg), or stage 3 hypertension (BP ≥ 180/110 mmHg).[21]

Glucose and serum lipids were measured with the On Call Plus and Mission Cholesterol devices, respectively. All test measurements were directly taken from the devices in mg/dL, except for LDL, which was calculated using the Friedewald formula.[22]

Non-fasting measurements were obtained; thus, high glucose levels were considered as ≥ 160 mg/dL;[23] and DLP was diagnosed for those with LDL 130 mg/dL and/or triglycerides ≥ 175 mg/dL.[24]

For the diagnosis of SAH, DM, and DLP, at least one of the following criteria was considered: self-report of disease, made by the participants themselves, and/or use of anti-hypertensive drugs and/or BP ≥ 140x90 mmHg in the mean of casual measurements; use of oral hypoglycemic agents and/or insulin and/or occasional blood glucose ≥ 200 mg/dL; use of statin, fibrates, ezetimibe, and/or triglycerides ≥ 175 mg/dL, and/or LDL ≥ 130 mg/dL.

Disease awareness was assessed by physicians' self-report. Data on the frequency of SAH, DM and DLP were compared with that obtained in Brazilian National Health Survey (Pesquisa Nacional de Saúde, PNS)[25] e in the Surveillance System for Risk and Protective Factors for Chronic Diseases

by Telephone Survey (Sistema de Vigilância de Fatores de Risco para Doenças Crônicas Não Transmissíveis por Inquérito Telefônico, VIGITEL);[26] for this analysis, only participants' self-report was considered (reported data).

SAH was considered controlled with systolic BP < 140 mmHg and diastolic BP < 90 mmHg, DM with glucose < 200 mg/dL, and DLP with LDL < 130 mg/dL and triglycerides < 175 mg/dL.[21,23,24]

Statistical analysis

Data were typed on the Excel for Mac software, version 16.30, and analyzed with Stata statistical analysis software, version 14. Descriptive statistics was expressed as mean, standard deviation, and absolute and relative frequencies.

Ethical aspects

The project was developed by the FUNCOR of the SBC, 2016/2017 term, and was approved by the Research Ethics Committee of IDPC, under number 2.016.859. All participants signed an ICF before any study procedure, in compliance with Resolution 466/2012.

Results

A total of 555 cardiologists were assessed, with a mean age of 47.2±11.7 years, of which 159 (28.6%) were from Central-West Region of Brazil, 147 (26.5%) from the Northeast Region, 103 (18.6%) from the North Region, 103 (18.6%) from Southeast Region, and 43 (7.7%) from the South Region.

Most study participants were male, were physically active, with a mean physical activity time of 200.0±106.8 minutes per week, did not smoke, and consumed alcohol (Table 1).

According to the measurements taken during the interview, most physicians presented with BP levels into the pre-hypertension category, and glucose, LDL, and triglycerides levels within normal range (Table 2).

The prevalence of SAH was 32.4% of participants (n=180); of these, 57.2% (n=103) were aware of their condition, and 48.3% (n=87) had their BP controlled. The prevalence of DM was 5.9% (n=33) of participants; of these, 45.5% (n=15) were aware of their condition, and 78.8% (n=26) had their glucose levels within normal range. DLP showed rates of prevalence, awareness, and control of 49.7% (n=276), 49.6% (n=137), and 31.1% (n=86), respectively (Figure 1).

With regard to cardiovascular outcomes, 4 (0.72%) cardiologists reported to have suffered an AMI, and 1 (0.18%) reported to have suffered a stroke. All four physicians with diagnosed coronary artery disease were on antiplatelet therapy.

Table 3 shows the frequencies of CVRF and cardiovascular outcomes of PNS,[25] VIGITEL,[26] and findings from the present study, considering only self-reported diseases.

Discussion

This is the first Brazilian study to assess cardiologists with CSD from the five geographical regions for the presence of CVRF and life habits. These cardiologists showed a very low prevalence of sedentary lifestyle and smoking, and a higher prevalence of alcohol consumption compared with studies that assessed the general population, such as PNS[25] and VIGITEL,[26] as well as a higher prevalence of DLP, a slightly lower prevalence of SAH, and a lower prevalence of DM. However, the rates of awareness of SAH, DM and DLP and the rates of control of SAH and DLP were low, considering that the study population consisted of cardiologists, which are supposed to understand the importance of controlling CVRF.

In the Brazilian population, the prevalence of SAH ranges from 30% to 36%;[27,28] the prevalence of DM is 11.4%;[29] and the prevalence of DLP is divided into hypercholesterolemia, with a prevalence of approximately 45.5%,[30] and hypertriglyceridemia, with a prevalence from 26.5% to 31. 2% in Latin America.[31,32] Furthermore, the prevalence of excess weight (overweight/obesity) in Brazil is 57% in men and 43% in women.[33] In the present study group, considering reported and measured data, the diagnosis rate was 32.4% for SAH, 4.9% for DM, 51.7% for DLP (hypercholesterolemia and/or hypertriglyceridemia), and 56% for excess weight (67.1% in men and 32.2% in women).

Lack of awareness of these CVRF is known to be high in the general population, but strikingly, it is also high among cardiologists, which lead us to consider that these professionals neglect their own health care. This delay in disease awareness, early diagnosis, and appropriate treatment may increased the risk of related outcomes.[34]

Health education to the lay population is knowingly able to improve live habits, leading to a decrease in cardiovascular diseases.[35] Hence, there was the questioning on the quality of cardiologists' self-care, since they are the bearers of this scientific knowledge. Medical students assessed for CVRF had a similar prevalence than that of the general population of the same age, except for higher rates of sedentary lifestyle and higher BMI, thus raising a discussion on the extensive workload of the course, which may influence on the low time availability for the practice of healthy life habits, compared with other young adults.[36] In another group of medical students, obesity rates were lower compared with those of population of the same age, as well as better serum lipid levels, but they showed high consumption of fast food and alcohol, in addition to higher rates of sedentary lifestyle, which may also be explained by low time availability and the high level of stress related to the course.[37]

It is known that work routine may often have a negative impact on the adoption of health and wellbeing practices, even if the professional have knowledge on the theme, such as health care professionals.[38] The work in this area requires working in night shifts, and professionals often have more than one job. Therefore, they have difficulty in practicing regular physical activity or prioritizing nutritionally balanced meals.

Conversely, the same discussion may be raised without the need of emphasizing the night shift as the most important harm, but considering only the excessive workload of these professionals, regardless of the period of the day. Two different groups assessed their professionals with regard to the prevalence of CVRF, including the entire multiprofessional

Table 1 – Sample description according to sex, lifestyle, and overall health conditions, n=555, 2017

Variable	n (%)
Sex	
Female	178 (32.1)
Male	377 (67.9)
Age	
< 40 years	183 (33.2)
≥ 40 years	368 (66.8)
Smoking	
Yes	03 (0.5)
No	492 (88.7)
Former smoker	60 (10.8)
Sedentary lifestyle	
Yes	127 (22.9)
No	428 (77.1)
Alcohol consumption	
Yes	434 (78.2)
No	121 (21.8)
Abdominal circumference	
Normal	285 (51.7)
High	266 (48.3)
Body mass index classification	
Non-overweight	243 (43.9)
Overweight	232 (41.9)
Obesity	79 (14.2)

Table 2 – Classification of cardiologists according to blood pressure, casual glucose, and serum lipids, 2017

Classification	n (%)
Blood pressure (n=555)	
Normal	204 (36.8)
Pre-hypertensive	264 (47.6)
Stage I hypertension	75 (13.5)
Stage II hypertension	08 (1.4)
Stage III hypertension	04 (0.7)
Casual glucose (n=555)	
Normal	548 (98.7)
High	07 (1.3)
LDL (n=538)	
Normal	411 (76.4)
High	127 (23.6)
Triglycerides (n=547)	
Normal	463 (84.6)
High	84 (15.4)

team in the assessment. In a general hospital, a high prevalence of CVRF were observed in all assessed professional categories.[39] Similar results were found in another group, with an even more worrisome situation, which is the lack of awareness of these individuals with regard to their already altered health satus.[40]

In the subgroups of cardiologists versus non-cardiologists physicians, no significant differences were observed in relation to serum levels of cholesterol and its fractions, as well as to Framingham risk score, but cardiologists consumed more alcohol, and both groups had a mean BMI above the ideal range.[41]

In a comparative analysis with the population surveys PNS[25] and VIGITEL,[26] the cardiologists assessed in the present study reported lower rates of smoking and sedentary lifestyle, but come more alcohol. Furthermore, considering only reported CVRF, cardiologists reported lower rates of SAH and DM, but higher rates of DLP. These data are worrisome, not only due to lack of awareness, but also because they call into question the credibility of surveys that use only reported data.

SAH, DM and DLP[42] are known to result from factors such as genetics and aging (non-modifiable), but are also related to life habits, and, within this context, individual with greater knowledge on cardiovascular risk factors are expected to have healthier habits.[43-45] With wide knowledge on the topic, cardiologists were expected to fully engage in good habits, so as to prevent these diseases, which is contrary to the findings in our sample with regard to alcohol consumption, but is consistent with findings related to smoking and physical activity. Similarly, a similar, or even higher, prevalence was found for the main CVRF, in comparison to the general population, except for DM.

Finally, the percentage of reported AMI (0.72%) and stroke (0.18%) in the sample was much lower than that of the general population, which may be related to the regular and frequent use of medications, due to physicians' knowledge on the appropriate treatment and ease of access to medications. Furthermore, mean age of the group was low (47.2 years) and may partly justify the low prevalence of AMI and stroke.[46]

The present study had the following limitations: the lack of HDL in the assessment for DLP, due to a limitation in the measuring device; lack of administration of instruments to assess physical activity and alcohol consumption, which may have overestimated these rates; and the fact that fasting biochemical tests were not obtained. Nonetheless, it is worth noting that equal devices were used to obtain both anthropometric measurements and BP value and blood biochemistry tests, with previous training of coinvestigators and general coordination of reference centers, showing an appropriate standardization of the procedure.

It is also worth emphasizing that the sample was not representative of cardiologists affiliated to the SBC, because this was a convenience sample, a fact that may relativize the results and the presented discussions. However, cardiologist from all over the country were assessed and, thus, this study represents a warning sign for the approach of the identified conditions and for the conduction of future studies with Brazilian cardiologists.

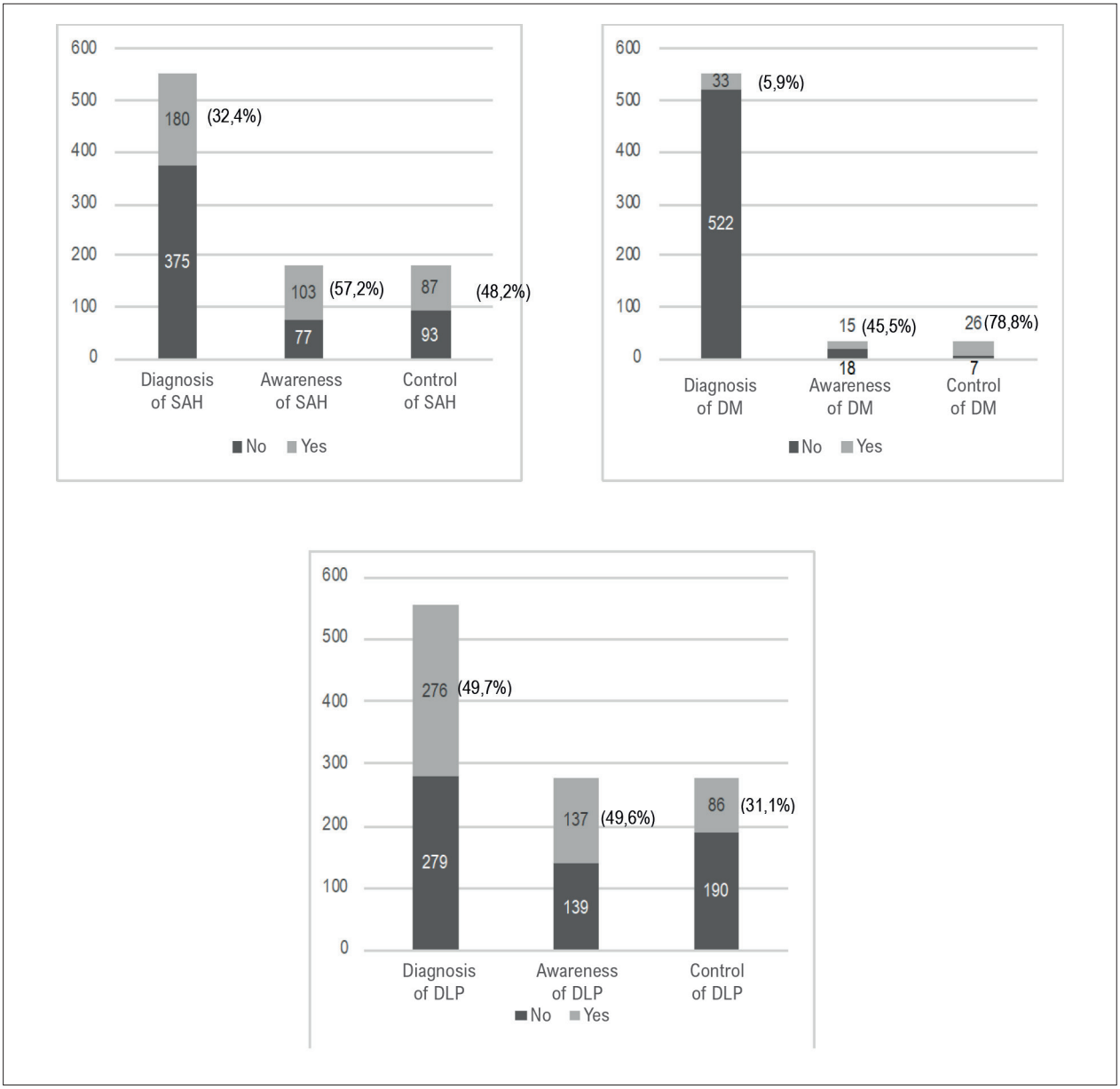


Figure 1 – *Prevalence of diagnosis, awareness, and control of SAH, DM and DLP in cardiologists, n=555, 2017. DLP: dyslipidemia; DM: diabetes mellitus; SAH: systemic arterial hypertension.*

Table 3 – Prevalence of risk factors and cardiovascular outcomes in the general population and among cardiologists. n = 555, 2017

	PNS	VIGITEL	Cardiologists (reported)	Cardiologists (measured)
Sedentary lifestyle	46	61.9	22.9	-
Alcohol consumption	24	17.9	78.2	-
Smoking	15	9.3	0.5	-
Arterial hypertension	21,4	24.7	18.6	32.4
Diabetes mellitus	6,2	7.7	2.7	5.9
Dyslipidemia	12,5	-	24.7	49.7
Acute myocardial infarction	4,2	-	0.7	-
Stroke	1,5	-	0.2	-

Source: PNS[25], VIGITEL 2018[26]

Conclusion

Most cardiologists were male, were physically active, did not smoke, consumed alcohol, and had a significant prevalence of SAH, DM and DLP, similar to those observed in other surveys with Brazilian populations. However, although cardiologist have knowledge on these CVRF, approximately a half of them were aware of these conditions and were with their pressure controlled; additionally, one third had their lipid levels within normal values, but most had their glucose levels controlled. Study findings represent a warning sign for the adequate approach of CVRF among Brazilian cardiologists and point to the need of future studies.

Coinvestigators

Alberto de Almeida Las Casas Júnior (Goiás), Alexandre Jorge de Andrade Negri (Paraíba), Andrés Gustavo Sánchez Esteva (Tocantins), Antônio Carlos Avanza Junior (Espírito Santo), Christiano Henrique Souza Pereira (Mato Grosso do Sul), Claudine Maria Alves Feio (Pará), Daniela Martins Lessa Barreto (Alagoas), Diana Patrícia Lamprea Sepúlveda (Pernambuco), Érika Maria Gonçalves Campana (Rio de Janeiro), Evandro Guimarães de Souza (Minas Gerais), Ezilaine Nascimento Rosa (Mato Grosso), Fátima Elizabeth Fonseca de Oliveira Negri (Paraíba), Harry Corrêa Filho (Santa Catarina), João Paulo Fernandes Caixeta (Goiás), João Roberto Gemelli (Rondônia), Joilma Silva Prazeres Tobias (Maranhão), José Fernando Vilela Martin (São Paulo), Juan Carlos Yugar Toledo (São Paulo), Lara Araújo Dias (Goiás), Maurício Pimentel (Rio Grande do Sul), Nivaldo Menezes Filgueiras Filho (Bahia), Sandra Andrade Mendonça Hilgemberg (Rio Grande do Norte), Sílvio Henrique Barberato (Paraná), Simone Nascimento dos Santos (Distrito Federal), Thaynara de Moraes Pacheco (Goiás).

Author contributions

Conception and design of the research: Amodeo C, Martinez T, Brandão AA, Barroso WKS; Acquisition of data: Teixeira MEF, Vitorino PVO, Barroso WKS; Analysis and interpretation of the data: Teixeira MEF, Vitorino PVO, Amodeo C, Martinez T, Brandão AA, Barbosa ECD, Feitosa ADM, Barroso WKS; Statistical analysis: Teixeira MEF, Vitorino PVO, Souza ALL, Barroso WKS; Obtaining financing: Amodeo C, Martinez T, Barroso WKS; Writing of the manuscript: Teixeira MEF, Vitorino PVO, Brandão AA, Barbosa ECD, Feitosa ADM, Jardim PCBV, Souza ALL, Barroso WKS; Critical revision of the manuscript for intellectual content: Teixeira MEF, Vitorino PVO, Amodeo C, Martinez T, Brandão AA, Barbosa ECD, Feitosa ADM, Jardim PCBV, Souza ALL, Barroso WKS.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by Indústria Farmacêutica EMS and equipment Medlevesson and Omron.

Study Association

This article is part of the thesis of master submitted by Maria Emilia Figueiredo Teixeira, from Pós-graduação em Ciências da Saúde - UFG.

References

1. Vos T, Abajobir AA, Abate KH, Abbafati C, Abbas KM, Abd-Allah F, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 328 diseases and injuries for 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet. 2017 Sep 16;390(10100):1211-59.
2. Masana L, Ros E, Sudano I, Angoulvant D, Ibarretxe Gerediaga D, Murga Eizagaechevarria N, et al. Is there a role for lifestyle changes in cardiovascular prevention? What, when and how. Atheroscler Suppl. 2017 Apr; 26: 2-15.
3. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. Lancet. 2002 Dec 14;360(9349):1903-13.
4. Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, et al. Clinical practice guidelines for the management of hypertension in the community a statement by the American Society of Hypertension and the International Society of Hypertension. J Hypertens. 2014 Jan;32(1):3-15.
5. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018 Sep 1;39(33):3021-104.
6. Ribeiro RQ. Cardiologista: um Prometeu acorrentado. Arq Bras Cardiol. 2010 Jul;95(1):e24-5.
7. Mesquita ET, Correia ETO, Barbetta LMDS. Profile of Brazilian Cardiologists: An Overview of Female Leadership in Cardiology and Stress - Challenges for the Next Decade. Arq Bras Cardiol. 2019 08 8;113(1):69-70.
8. Jardim TV, Sousa AL, Povoa TI, Barroso WK, Chinem B, Jardim L, et al. The natural history of cardiovascular risk factors in health professionals: 20-year follow-up. BMC Public Health. 2015 Nov 11;15:1111.
9. Dioguardi G, Pimenta J, Knoplich J, Ghorayeb N, Ramos LR, Giannini SD. Fatores de risco para doenças cardiovasculares em médicos: dados preliminares do projeto vidam da associação paulista de medicina. Arq. Bras. Cardiol. 1994 Jul;62:383-8.
10. Scheffer M, Biancarelli A, Cassenote A. Demografia médica no Brasil 2015. [Internet]. São Paulo: Universidade de São Paulo; Conselho Regional de Medicina do Estado de São Paulo; Conselho Federal de Medicina; 2015. 285p. [citado 30 Jun 2017]. Disponível em: http://www.usp.br/agen/wp-content/uploads/DemografiaMedica30nov20153.pdf
11. Sociedade Brasileira de Cardiologia. CJTEC - Título de Especialista em Cardiologia [Internet]. 2018 [citado 15 de novembro de 2019]. Disponível em: http://educacao.cardiol.br/cjtec/especialistas.asp
12. World Health Organization. Global recommendations on physical activity for health. World Health Organization; 2010.
13. Peixoto MR, Benício MH, Jardim PC. [Validity of self-reported weight and height: the Goiânia study, Brazil]. Rev Saude Publica. 2006 Dec;40(6):1065-72.

14. Lohman TG, Roche AF, Martorell R. Anthropometric standardization reference manual. Champaign: Human Kinetics; 1988).

15. Ross WD, Drinkwater DT, Bailey DA, Marshall GR, Leahy RM. Kinanthropometry: traditions and new perspectives. In: Ostyn M, Beunen G, Simons J, editors. Kinanthropometry II. Baltimore: University Park Press, 1980:3-26.

16. Calle EE, Thun MJ, Petrelli JM, Rodriguez C, Heath CW. Body-mass index and mortality in a prospective cohort of U.S. adults. N Engl J Med. 1999 Oct 7;341(15):1097-105.

17. World Health Organization. Waist circumference and waist–hip ratio: report of a WHO expert consultation. Geneva: World Health Organization; 2008.

18. Dabl® Educational Trust Limited. Comparison of the Omron HBP-1100 with the Omron HBP-1300 Devices [Internet]. 2014 [citado 15 de novembro de 2019]. Available at: www.dableducational.orgFormDET6140526

19. Cao X, Song C, Guo L, Yang J, Deng S, Xu Y, et al. Quality Control and Validation of Oscillometric Blood Pressure Measurements Taken During an Epidemiological Investigation. Medicine (Baltimore). 2015 Sep;94(37):e1475.

20. Meng L, Zhao D, Pan Y, Ding W, Wei Q, Li H, et al. Validation of Omron HBP-1300 professional blood pressure monitor based on auscultation in children and adults. BMC Cardiovasc Disord. 2016 Jan 13;16:9.

21. Malachias MV. 7th Brazilian Guideline of Arterial Hypertension: Presentatio. Arq Bras Cardiol. 2016 09;107(3 Suppl 3):0.

22. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972 Jun;18(6):499-502.

23. Sociedade Brasileira de Diabetes. Diretrizes da Sociedade Brasileira de Diabetes (2017-2018). São Paulo: Editora Clannad; 2017.

24. Faludi A, Izar M, Saraiva J, Chacra A, Bianco H, Afiune Neto A, et al. Atualização da Diretriz Brasileira de dislipidemias e prevenção da aterosclerose - 2017. Arq Bras Cardiol. 2017;109(1).

25. Instituto Brasileiro de Geografia e Estatística. Pesquisa Nacional de Saúde 2013: percepção do estado de saúde, estilos de vida e doenças crônicas - Brasil, Grandes Regiões e Unidades da Federação [Internet]. Rio de Janeiro: Instituto Brasileiro de Geografia e Estatística; 2014 [citado 2020 Jan 9]. 181 p. Disponível em: ftp://ftp.ibge.gov.br/PNS/2013/pns2013.pdf

26. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância de Doenças e Agravos não Transmissíveis e Promoção da Saúde. Vigitel Brasil 2018: vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico: estimativas sobre frequência e distribuição sociodemográfica de fatores de risco e proteção para doenças crônicas nas capitais dos 26 estados brasileiros e no Distrito Federal em 2018. Brasília: Ministério da Saúde, 2019, 131 p.

27. Picon RV, Fuchs FD, Moreira LB, Riegel G, Fuchs SC. Trends in prevalence of hypertension in Brazil: a systematic review with meta-analysis. PLoS ONE. 2012;7(10):e48255.

28. Chor D, Pinho Ribeiro AL, Sá Carvalho M, Duncan BB, Andrade Lotufo P, Araújo Nobre A, et al. Prevalence, Awareness, Treatment and Influence of Socioeconomic Variables on Control of High Blood Pressure: Results of the ELSA-Brasil Study. PLoS ONE. 2015;10(6):e0127382.

29. International Diabetes Federation. *IDF Diabetes Atlas, 9th edn.* Brussels, Belgium: 2019. Available at: https://www.diabetesatlas.org

30. Lotufo PA, Santos RD, Figueiredo RM, Pereira AC, Mill JG, Alvim SM, et al. Prevalence, awareness, treatment, and control of high low-density lipoprotein cholesterol in Brazil: Baseline of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). J Clin Lipidol. 2016 May-Jun;10(3):568-76.

31. Miranda JJ, Herrera VM, Chirinos JA, Gómez LF, Perel P, Pichardo R, et al. Major cardiovascular risk factors in Latin America: a comparison with the United States. The Latin American Consortium of Studies in Obesity (LASO). PLoS ONE. 2013;8(1): e54056.

32. Ponte-Negretti CI, Isea-Perez JE, Lorenzatti AJ, Lopez-Jaramillo P, Wyss-Q FS, Pintó X, et al. Atherogenic Dyslipidemia in Latin America: Prevalence, causes and treatment: Expert's position paper made by The Latin American Academy for the Study of Lipids (ALALIP) Endorsed by the Inter-American Society of Cardiology (IASC), the South American Society of Cardiology (SSC), the Pan-American College of Endothelium (PACE), and the International Atherosclerosis Society (IAS). Int J Cardiol. 2017 Sep 15;243:516-22.

33. Rtveladze K, Marsh T, Webber L, Kilpi F, Levy D, Conde W, et al. Health and economic burden of obesity in Brazil. PLoS ONE. 2013;8(7): e68785.

34. Precoma D, Oliveira GMA, Simão AF, Dutra OP, Coelho CR, Izar MCO, Povoa RMD, et al, Sociedade Brasileira de Cardiologia. Atualização da Diretriz de Prevenção Cardiovascular da Sociedade Brasileira de Cardiologia - 2019. Arq Bras Cardiol. 2019;113(4):787-891.

35. Dahrouge S, Kaczorowski J, Dolovich L, Paterson M, Thabane L, Tu K, et al. Long-term outcomes of cluster randomized trial to improve cardiovascular health at population level: The Cardiovascular Health Awareness Program (CHAP). PLoS ONE. 2018;13(9): e0201802.

36. Schmidt MI, Duncan BB, Mill JG, Lotufo PA, Chor D, Barreto SM, et al. Cohort Profile: Longitudinal Study of Adult Health (ELSA-Brasil). Int J Epidemiol. 2015 Feb;44(1):68-75.

37. Coelho VG, Caetano LF, Liberatore Júnior Rdel R, Cordeiro JA, Souza DR. Perfil lipídico e fatores de risco para doenças cardiovasculares em estudantes de medicina. Arq Bras Cardiol. 2005 Jul;85(1):57-62.

38. Faganello LS, Pimentel M, Polanczyk CA, Zimerman T, Malachias MVB, Dutra OP, et al. O Perfil do Cardiologista Brasileiro - Uma Amostra de Sócios da Sociedade Brasileira de Cardiologia. Arq Bras Cardiol. 2019 06 27;113(1):62-8.

39. Rodríguez-Reyes RR, Navarro-Zarza JE, Tello-Divicino TL, Parra-Rojas I, Zaragoza-García O, Guzmán-Guzmán IP. [Detection of cardiovascular risk in healthcare workers on the basis of WHO/JNC 7/ATP III criteria]. Rev Med Inst Mex Seguro Soc. 2017 May-Jun;55(3):300-8.

40. Oğuz A, Sağun G, Uzunlulu M, Alpaslan B, Yorulmaz E, Tekiner E, et al. Frequency of abdominal obesity and metabolic syndrome in healthcare workers and their awareness levels about these entities. Turk Kardiyol Dern Ars. 2008 Jul;36(5):302-9.

41. Marochi LH, Campos CW, Marcante FP, Moreira DM. Comparação de fatores de risco cardiovascular entre médicos cardiologistas e não cardiologistas. Rev Bras Cardiol. 2013;26(4):248-52.

42. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2020 Jan 1;41(1):111-88.

43. Appel LJ, Brands MW, Daniels SR, Karanja N, Elmer PJ, Sacks FM. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. Hypertension. 2006 Feb;47(2):296-308.

44. Backer G. Epidemiology and prevention of cardiovascular disease: Quo vadis. Eur J Prev Cardiol. 2017 05;24(7):768-72.

45. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J. 2020 Jan 7;41(2):255-323.

46. Schmidt MI, Hoffmann JF, Fátima Sander Diniz M, Lotufo PA, Griep RH, Bensenor IM, et al. High prevalence of diabetes and intermediate hyperglycemia - The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). Diabetol Metab Syndr. 2014;6:123.

Cardiovascular Risk Factors in Cardiologists Certified by the Brazilian Society of Cardiology: Lessons to be Learned

Claudio Tinoco Mesquita[1,2,3] *and Wilter dos Santos Ker*[2,3]

Setor de Medicina Nuclear - Hospital Universitário Antônio Pedro (HUAP)/Ebserh - Universidade Federal Fluminense (UFF), Niterói,[1] *RJ - Brazil*
Serviço de Medicina Nuclear - Hospital Pró-Cardíaco,[2] *Rio de Janeiro, RJ - Brazil*
Hospital Vitória,[3] *Rio de Janeiro, RJ – Brazil*

Short Editorial related to the article: Cardiovascular Risk Factors In Cardiology Specialists From The Brazilian Society of Cardiology

Cardiovascular diseases (CVD) remain the leading cause of death in the world. Risk factors such as systemic arterial hypertension (SAH), diabetes mellitus (DM), dyslipidemia, obesity, smoking and alcoholism associated with sedentary behavior, sleep deprivation, stress and family history favor atherosclerosis. The complexity of pathophysiology in the process of atherosclerosis formation and the variety of risk factors for artery disease have important impacts on mortality.[1-3] SAH is an important risk factor, being the most prevalent for CVD and its relationship is the result of vascular lesions that cause hyperplasia and hypertrophy of the middle layer of the vessel. Cardiovascular disease is the main cause of mortality and morbidity in people with diabetes. It is the result of hyperglycemia and insulin resistance, leading to chronic inflammation, oxidative stress and, ultimately, endothelial dysfunction. DM has increased significantly in recent years, making it one of the main causes of mortality. Insulin resistance promotes dyslipidemia, accelerating atherosclerosis in diabetic patients.[4-7] Obesity prevalence has grown greatly in recent decades. It is a complex condition that has a great impact on cardiovascular diseases and plays an important role in affecting risk factors (SAH, DM and dyslipidemia). Sudden death is increased in obese patients, usually by frequent and complex ventricular arrhythmias.[11] Smoking, alcohol intake and sedentary lifestyle are related to increased cardiovascular risk affecting all phases of atherosclerosis.[9,10] Unhealthy eating is related to factors that interfere with the prevention and control of CVD, being of great importance for early mortality around the world. The adoption of healthy habits requires constant personal efforts and resilience.[8-10] Improvement in lifestyle associated with healthy eating provides new perspectives on cardiovascular prevention. Physical activity has positive effects on lipid metabolism, glucose, and blood pressure combined with new classes of drugs to control risk factors has resulted in lower cardiovascular outcomes. Tobacco control is an important instrument in primary prevention which, through continuing education in recent years, has seen an important reduction in the number of people dependent on smoking.[8-11]

In a new study with cardiologists, Teixeira et al. found lower prevalence of sedentary lifestyle and smoking, but a higher prevalence of alcohol consumption. The prevalence of dyslipidemia was higher than SAH and DM. Although specialists had greater knowledge about the disease, it was not possible to observe healthier habits than the rest of the population.[12-14] In contrast, in Canada, a cohort study of 17,071 practicing physicians and 5,306,038 members of the general population found that physicians used fewer guideline-recommended preventive services and had lower rates of cardiac risk factors. After 8 years' follow-up, physicians had a substantially lower risk of adverse outcomes than the general population.[15] These results could lead us to speculate about the possible causes for these differences. A stressful lifestyle and excessive working hours linked to medical practice in Brazil could be responsible for part of these findings.

The implementation of lifestyle changes, primary and secondary prevention combined with appropriate therapy and early diagnosis is fundamental to reduce CVD. Despite the level of knowledge of health professionals, little is known about their risk factors for CVD. In Brazil, cardiologists play an important role in promoting prevention and treatment of cardiovascular diseases.[16] Improvements in clinical guidelines have brought significant clinical benefits to the prevention of CVD. However, there is an important unmet need: to better understand the factors that impact Brazilian cardiologists' habits, and to improve their risk factors .[12-15]

keywords

Coronary Artery Disease/mortality; Atherosclerosis; Dyslipidemias; Obesity; Diabetes Mellitus; Risk Factors; Cardiologists.

Mailing Address: Claudio Tinoco Mesquita •
Hospital Universitário Antonio Pedro, Setor de Medicina Nuclear, Departamento de Radiologia - Av. Marques do Paraná, 303. Postal Code 24070-035, Niterói, RJ - Brazil
E-mail: claudiotinocomesquita@id.uff.br

DOI: https://doi.org/10.36660/abc.20210153

References

1. Bernoche C, Timerman S, Polastri TF, Giannetti NS, Siqueira AWS, Piscopo A, et al. Atualização da Diretriz de Ressuscitação Cardiopulmonar e Cuidados Cardiovasculares de Emergência da Sociedade Brasileira de Cardiologia - 2019. *Arq. Bras. Cardiol.* 2019;113(3):449-63.
2. Marochi LH, Campos CW, Marcante FP, Moreira DM. Comparação de fatores de risco cardiovascular entre médicos cardiologistas e não cardiologistas. Rev Bras Cardiol. 2013;26(4):248-52.
3. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Diretriz sobre a Prevenção Primária de Doenças Cardiovasculares: Um Relatório do American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019 ;74(10):e177-e232.
4. Koene RJ, Prizment AE, Blaes A, Konety SH. Fatores de Risco Compartilhados em Doenças Cardiovasculares e Câncer. *Circulation*. 2016;133(11):1104-14.
5. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, Delgado V, et al. 2019 ESC Diretrizes sobre diabetes, pré-diabetes e doenças cardiovasculares desenvolvidas em colaboração com a EASD. Eur Heart J. 2020 Jan 7;41(2):255-323.
6. Fuchs FD, Whelton PK. High Blood Pressure and Cardiovascular Disease. Hypertension. 2020;75(2):285-92.
7. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Efeito de fatores de risco potencialmente modificáveis associados ao infarto do miocárdio em 52 países (o estudo INTERHEART): estudo de caso-controle. Lancet. 2004;364(9438):937-52.
8. Anton SD, Moehl K, Donahoo WT, Marosi M, Lee AS; Mainows 3rd SG, et al. Invertendo o interruptor metabólico: Compreender e aplicar os benefícios para a saúde do jejum. Obesity (Silver Spring)2018;26(2):254-68.
9. Meyers DG, Neuberger JS, He J. Efeito cardiovascular das proibições ao tabagismo em local público Meyers DG, Neuberger JS e He J. Efeito cardiovascular das proibições ao tabagismo em locais públicos: Revisão sistemática e meta-análise. J Am Coll Cardiol 2009;54(14):1249-55.
10. Kadhum M, Jaffery A, Haq A, et al. Medindo os efeitos cardiovasculares agudos do tabagismo de shisha: Um estudo transversal. JRSM Open 2014; 5: 2054270414531127.
11. Swinburn BA, Kraak VI, Allender S, Atkins VJ, Baker PI, Bogard JR, et al. The Global Syndemic of Obesity, Undernutrition, and Climate Change: The Lancet Commission report. Lancet. 2019;393(10173):791-846.
12. Dahrouge S, Kaczorowski J, Dolovich L, Paterson M, Thabane L, Tu K, et al. Resultados de longo prazo de ensaio randomizado de cluster para melhorar a saúde cardiovascular no nível populacional: O Programa de Conscientização da Saúde Cardiovascular (CHAP). PLos UM. 2018;13(9): e0201802.
13. Schmidt MI, Duncan BB, Mill JG, Lotufo PA, Chor D, Barreto SM, et al. Coorte Perfil: Estudo Longitudinal de Saúde adulta (ELSA-Brasil). Int J Epidemiol. 2015 Fev;44(1):68-75.
14. Teixeira MEF, Vitorino PVO, Amodeo C, Martinez T, Brandão AA, Barbosa ECD, et al. Fatores de Risco Cardiovascular em Cardiologistas Especialistas pela Sociedade Brasileira de Cardiologia. Arq Bras Cardiol. 2021; 116(4):774-781.
15. Ko DT, Chu A, Austin PC, Johnston S, Nallamothu BK, Roifman I, Tusevljak N, Udell JA, Frank E. Comparison of Cardiovascular Risk Factors and Outcomes Among Practicing Physicians vs the General Population in Ontario, Canada. JAMA Netw Open. 2019 Nov 1;2(11):e1915983.
16. Mesquita ET, Correia ETO, Barbetta LMDS. Perfil dos Cardiologistas Brasileiros: Visão Geral da Liderança Feminina em Cardiologia e Estresse - Desafios para a Próxima Década. Arq Bras Cardiol.2021; 116(4):784-792.

Effects of Late Aerobic Exercise on Cardiac Remodeling of Rats with Small-Sized Myocardial Infarction

Lidiane M. Souza,[1] Marina P. Okoshi,[1] Mariana J. Gomes,[1] Mariana Gatto,[1] Eder A. Rodrigues,[1] Thierres H. D. Pontes,[1] Felipe C. Damatto,[1] Leiliane R. S. Oliveira,[1] Patrícia Aparecida Borim,[1] Aline R. R. Lima,[1] Leonardo A. M. Zornoff,[1] Katashi Okoshi,[1] Luana U. Pagan[1]

Faculdade de Medicina de Botucatu, Universidade Estadual Paulista "Júlio de Mesquita Filho" (UNESP),[1] Botucatu, SP – Brazil

Abstract

Background: Physical exercise has been considered an important non-pharmacological therapy for the prevention and treatment of cardiovascular diseases. However, its effects on minor cardiac remodeling are not clear.

Objective: To evaluate the influence of aerobic exercise on the functional capacity, cardiac structure, left ventricular (LV) function, and gene expression of NADPH oxidase subunits in rats with small-sized myocardial infarction (MI).

Methods: Three months after MI induction, Wistar rats were divided into three groups: Sham; sedentary MI (MI-SED); and aerobic exercised MI (MI-AE). The rats exercised on a treadmill three times a week for 12 weeks. An echocardiogram was performed before and after training. The infarction size was evaluated by histology, and gene expression was assessed by RT-PCR. The significance level for statistical analysis was set at 5%.

Results: Rats with MI lower than 30% of the LV total area were included in the study. Functional capacity was higher in MI-AE than in Sham and MI-SED rats. The infarction size did not differ between groups. Infarcted rats had increased LV diastolic and systolic diameter, left atrial diameter, and LV mass, with systolic dysfunction. Relative wall thickness was lower in MI-SED than in the MI-AE and Sham groups. Gene expression of the NADPH oxidase subunits NOX2, NOX4, $p22^{phox}$, and $p47^{phox}$ did not differ between groups.

Conclusion: Small-sized MI changes cardiac structure and LV systolic function. Late aerobic exercise is able to improve functional capacity and cardiac remodeling by preserving the left ventricular geometry. NADPH oxidase subunits gene expression is not involved in cardiac remodeling or modulated by aerobic exercise in rats with small-sized MI. (Arq Bras Cardiol. 2021; 116(4):784-792)

Keywords: Exercise, Physical Exercise; Ventricular Dysfunction; Myocardial Infarction; Rats; Ventricular Remodeling; Echocardiography/methods; NADPH Oxidase.

Introduction

Cardiovascular diseases are a leading cause of death worldwide; in this class of diseases, myocardial infarction (MI) is the main cause of morbidity and mortality.[1]

Acute MI leads to cardiac remodeling, which is defined as abnormalities in genome expression resulting in molecular, cellular and interstitial changes that manifest clinically as alterations in heart size, shape and function.[2] Oxidative stress, characterized by an imbalance between reactive oxygen species production and antioxidant systems, is often observed during cardiac remodeling.[3] The nicotinamide adenine dinucleotide phosphate (NADPH) oxidase complex, an important source of cellular reactive oxygen species production,[4] is usually increased after MI.[5]

In recent decades, physical exercise has emerged as an important non-pharmacological therapy for preventing and treating several cardiovascular diseases.[6] Aerobic exercise has been the focus of many studies for attenuating MI-induced cardiac remodeling and improving functional capacity and quality of life.[7-10]

Animal MI models are widely used for studying the pathophysiology and treatment of cardiac remodeling. Most studies evaluating the effects of exercise on post-MI cardiac changes have used rodents with large infarcted areas, usually more than 30% of the total left ventricle (LV) area.[8,11-14] However, it is not clear yet whether aerobic exercise is useful to attenuate cardiac changes following smaller-size LV infarction. In this study we aimed to evaluate the influence of aerobic physical exercise on functional capacity, cardiac structures, LV function, and NADPH oxidase subunit gene expression in rodents with small-sized MI.

Mailing Address: Luana U. Pagan •
Universidade Estadual Paulista Júlio de Mesquita Filho Câmpus de Botucatu Faculdade de Medicina - Clinica médica - Av. Prof. Mário Rubens Guimarães Montenegro, s/n. Postal Code 18618-687, Botucatu, SP – Brazil
E-mail: luanapagan@alunos.fmb.unesp.br
Manuscript received November 18, 2019, revised manuscript February 26, 2020, accepted March 16/03/2020.

DOI: https://doi.org/10.36660/abc.20190813

Materials and methods

Experimental animals

Male Wistar rats weighing 200-250 g were purchased from the Central Animal House, Botucatu Medical School, UNESP. All animals were kept in a temperature-controlled room at 24 ± 2º C and put on a 12-hour light/dark cycle in collective cages (three per cage). Food and water were supplied *ad libitum*.

All experiments and procedures were approved by the Animal Experimentation Ethics Committee of the Botucatu Medical School, UNESP, SP, Brazil, which follows the guidelines established by the Guide for the Care and Use of Laboratory Animals published by the U.S. National Institutes of Health, and Brazilian College for Animal Experimentation (protocol number 1237/2017).

MI was induced by ligating the left anterior descending coronary artery according to a previously described method.[3,14] Briefly, 60 rats were anesthetized with ketamine (60 mg/kg) and xylazine hydrochloride (1 mg/kg) and subjected to left lateral thoracotomy. After exteriorization of the heart, the left atrium was retracted to facilitate ligation of the coronary artery with a 5-0 monofilament nylon suture between the pulmonary outflow tract and the left atrium. The heart was then placed back in the thorax, the lungs inflated with positive pressure, and the thoracotomy was closed. Fifteen sham-operated animals were used as controls.

Three months later, the rats that survived were subjected to transthoracic echocardiogram and exercise testing and then assigned to three groups: Sham (n=15); sedentary MI (MI-SED, n=22) and aerobic exercised MI (MI-AE, n=21) for three months. Seventeen infarcted rats (28%) died during surgery or in the post-operative period. Initial echocardiogram results were used to assure that sedentary and exercise MI groups had the same degree of cardiac injury. At the end of the experimental period, the animals were again subjected to echocardiogram and exercise testing, and euthanized the next day. Previous studies have shown that the inclusion of 10 to 15 animals per group is sufficient to show differences in cardiac remodeling when comparing infarcted and Sham rats.[3,14]

Exercise testing

Functional capacity was evaluated before, 45 days after initiating exercise, and at the end of the experiment. Rats underwent 5 min/day an adaption to test environment for one week before evaluation. Each animal was tested individually. The test consisted of an initial 5-minute warm-up at 5 m/min on a treadmill. The rats were then subjected to exercise at 8 m/min followed by increments of 3 m/min every 3 minutes until exhaustion. Exhaustion was determined when the animal refused to run even after electric stimulation or was unable to coordinate steps.[15,16] The maximum running speed was recorded and total distance was calculated. Exercise test results from 45-day training were used to adjust exercise intensity.

Exercise training protocol

Exercise was performed on a treadmill three days/week for three months. There was an adaptation period, with a gradual increase in speed and exercise duration. Speed from the 1st to the 5th week was 5, 7.5, 10, 12 and 15 m/min. Exercise duration from the 1st to the 5th week was 10, 15, 25, 30 and 40 minutes. From the 6th week on, each session consisted of 40 minutes of running at 60% of maximum velocity reached in the treadmill exercise test. The protocol was adapted from Moreira et al.[17] After 45 days of aerobic exercise training, animals had their running performance reevaluated as to adjust exercise intensity.

Echocardiography

Cardiac structures and LV function were evaluated by transthoracic echocardiogram and tissue Doppler imaging using a commercially available echocardiograph (General Electric Medical Systems, Vivid S6 model, Tirat Carmel, Israel) equipped with a 5–11.5 MHz multifrequency transducer, as previously described.[18-20] The animals were anesthetized with ketamine (50 mg/kg) and xylazine hydrochloride (1 mg/kg *i.p.*), and placed in left lateral decubitus. All cardiac structures were manually measured by the same observer (KO). Results were the mean of at least five cardiac cycles on M-mode tracings. The following structural variables were measured: left atrium diameter (LA), LV diastolic and systolic diameters (LVDD and LVSD, respectively), LV diastolic posterior wall thickness (DPWT) and aortic diameter (AO). Left ventricular mass (LVM) was calculated using the formula [(LVDD + DPWT + DSWT)^3 − LVDD^3] × 1.04. LV relative wall thickness (RWT) was calculated with the formula 2 × DPWT/LVDD. Systolic function was assessed by the following parameters: endocardial fractional shortening (EFS), posterior wall shortening velocity (PWSV), fractional area change (FAC), myocardial performance index (Tei index), and systolic velocity of the mitral annulus (S' wave) obtained by tissue Doppler imaging. The diastolic function was analyzed by early and late diastolic mitral inflow velocities (E and A waves), E/A ratio, isovolumetric relaxation time (IVRT), early diastolic (E') and late diastolic (A') velocity of the mitral annulus (arithmetic average travel speeds of the lateral and septal walls), and E/E' ratio.

Collection of tissues for analysis

One day after final echocardiogram, the animals were weighed, anesthetized with intraperitoneal sodium thiopental (180 mg/kg) and euthanized. Their hearts were removed by thoracotomy. The lung, atria and ventricles were dissected and weighed. Fragments of LV were frozen in liquid nitrogen and stored at -80 °C for posterior analysis.

Morphologic study

LV samples were fixed in a 10% buffered formalin solution for 24 hours, then washed in water and transferred to a solution with ethanol, according to a previously described method.[21]

To calculate infarction size, the LV was cut at a distance of 5 to 6 mm from the apex.[22] Heart slices were stained with picrosirius red (PSR) and examined under a compound microscope (Leica DM LS; Nussloch, Germany) coupled to a computerized imaging analysis system (Media Cybernetics, Silver Spring, Maryland, USA).[23] The infarction size was calculated by dividing the sum of endocardial and epicardial infarcted ventricular lengths by the sum of the total (infarcted and viable myocardium) endocardial and epicardial ventricular circumferences.[14] Values were expressed as percentage of the total LV area. Only rats with small-sized MI

(<30% of total LV area) at histological evaluation were included in the study.

Cardiomyocyte diameters were assessed in LV transverse sections stained with hematoxylin-eosin. The smallest diameter of at least 50 cardiac fibers with the nucleus clearly identified was measured.[24]

Gene expression of NADPH oxidase subunits

Gene expression of NADPH oxidase subunits NOX2, NOX4, $p22^{phox}$, and $p47^{phox}$ and reference genes was analyzed by Real-Time Quantitative Reverse Transcription-Polymerase Chain Reaction (RT-PCR), as previously described.[25] Total RNA was extracted from LV samples with TRIzol Reagent (Invitrogen Life Technologies, Carlsbad, CA, USA) and treated with DNase I (Invitrogen Life Technologies). One microgram of RNA was reverse-transcribed using a High-Capacity cDNA Reverse Transcription kit, according to standard methods (Applied Biosystems, Foster City, CA, USA). Aliquots of cDNA were then submitted to real-time PCR using a customized assay containing sense and antisense primers and Taqman (Applied Biosystems, Foster City, CA, USA) probes specific to each gene: NOX2 (Rn00576710 m1), NOX4 (Rn00585380 m1), $p22^{phox}$ (Rn00577357 m1), and $p47^{phox}$ (Rn00586945 m1). Amplification and analysis were performed using the Step One Plus™ Real-Time PCR System (Applied Biosystems, Foster City, CA, USA). Expression data were normalized to reference gene expressions: cyclophilin (Rn00690933 m1) and GAPDH (Rn01775763 g1). Reactions were performed in triplicate and expression levels calculated based on the CT comparative method ($2^{-\Delta\Delta CT}$).

Statistical analyzes

Data normality was evaluated by the Shapiro-Wilk test. Comparisons between groups were performed by one-way analysis of variance (ANOVA), followed by the Bonferroni test for parametric variables, which are expressed as mean ± standard deviation. Non-parametric variables were compared using the Kruskal-Wallis test followed by Dunn's test, being expressed as median and percentiles. Infarction size was compared by the unpaired *Student t* test. Statistical analyzes were performed on the SigmaStat 12.0 software. The significance level was set at 5%.

Results

Experimental groups and anatomical parameters

At the beginning of the exercise protocol, the Sham group had 15 animals, MI-SED had 22, and MI-AE had 21. After histologic analysis, the rats with infarction size ≥ 30% of total LV area (9 in MI-SED and 9 in MI-AE group) were excluded from the study. Only one rat from MI-SED died during the exercise protocol. Anatomical parameters are shown in Table 1. Final body weight did not differ between groups. Atria and right ventricle (RV) weights were higher in MI-AE than in Sham group. No differences between MI-AE and MI-SED groups were found.

Infarction size, assessed by LV histological analysis, did not differ between infarcted groups (MI-SED 18.7 ± 6.41; MI-AE 23.6 ± 6.14% of total LV area; p>0.05; Figure 1).

Echocardiographic evaluation

Before exercise, there were no differences in echocardiographic parameters between MI-AE and MI-SED groups (data not shown). Final echocardiographic structural data are listed in Table 2. Both infarcted groups had higher LV systolic and diastolic diameters, left atrial diameter, and LV mass compared to the Sham group. LV diastolic posterior wall thickness was higher in MI-AE than in Sham, and relative wall thickness was lower in MI-SED than in MI-AE and Sham groups. LV systolic function is shown in Table 3. Infarcted groups had lower fractional area change and endocardial fractional shortening, as well as higher Tei index when compared to Sham. LV diastolic function is presented in Table 4. E' (average and septal) wave was lower in both infarcted groups as related to the Sham group. MI-AE had lower E/A ratio than Sham. E'/A' ratio was lower in MI-SED than in Sham. No differences were observed between exercised and sedentary infarcted groups.

Functional capacity

Functional capacity did not differ between groups before exercise. At the end of the experiment, functional capacity was better in MI-AE than in the other groups (Figure 2).

Table 1 – Anatomical data

	SHAM (n=15)	MI-SED (n=12)	MI-AE (n=12)
BW (g)	536 ± 29.7	537 ± 66.8	529 ± 44.7
LV (g)	0.90 (0.87-0.97)	0.99 (0.93-1.03)	0.99 (0.90-1.11)
LV/BW (g/kg)	1.73 ± 0.10	1.90 ± 0.19	1.88 ± 0.23
RV (g)	0.23 ± 0.03	0.26 ± 0.04	0.29 ± 0.05*
RV/BW (g/kg)	0.43 ± 0.05	0.48 ± 0.07	0.54 ± 0.08*
Atrial weight (g)	0.10 (0.08-0.11)	0.13 (0.10-0.13)	0.13 (0.11-0.14)*
Atrial/BW (g/kg)	0.19 (0.15-0.22)	0.22 (0.19-0.24)	0.27 (0.22-0.28)*
Lung/BW (g/kg)	3.60 (3.19-3.70)	3.43 (3.09-3.72)	3.66 (3.58-4.13)

*Data are expressed as mean ± standard deviation or median and percentiles. MI-SED: sedentary myocardial infarction; MI-AE: aerobic exercise myocardial infarction; n: number of animals; BW: body weight; LV: left ventricle weight; RV: right ventricle weight. ANOVA and Bonferroni or Kruskal-Wallis and Dunn's test; *p<0.05 vs. Sham.*

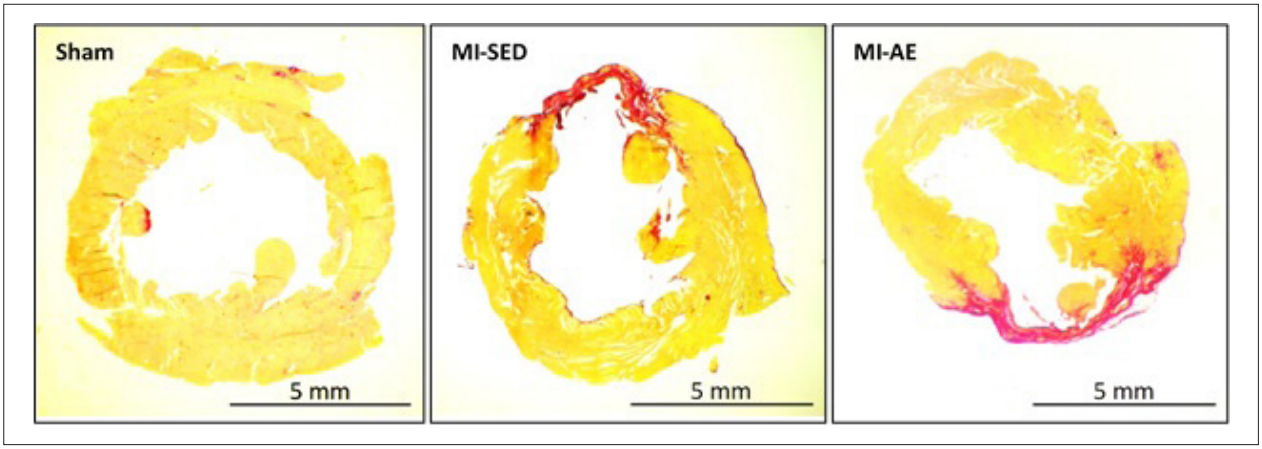


Figure 1 – *Figure 1 - Representative histological photos of picrosirius red-stained portions of left ventricles from the groups SHAM, sedentary myocardial infarction (MI-SED), and aerobic exercise myocardial infarction (MI-AE).*

Table 2 – Echocardiographic structural data

	SHAM (n=15)	MI-SED (n=10)	MI-AE (n=12)
HR (bpm)	267 ± 32.9	278 ± 19.7	290 ± 28.7
LVDD (mm)	8.19 ± 0.44	9.99 ± 0.81*	9.93 ± 0.98*
LVSD (mm)	4.13 (3.96-4.30)	7.16 (6.60-8.21)*	7.25 (6.73-8.16)*
DPWT (mm)	1.42 (1.40-1.45)	1.53 (1.45-1.61)	1.67 (1.58-1.85)*
AO (mm)	4.20 ± 0.15	4.12 ± 0.22	4.13 ± 0.25
LA (mm)	5.68 ± 0.42	6.71 ± 0.75*	6.97 ± 1.07*
LA/AO	1.37 (1.30-1.42)	1.64 (1.47-1.79)*	1.66 (1.47-1.82)*
LVDD/BW (mm/kg)	15.2 (14.8-16.3)	17.9 (16.9-20.3)*	18.5 (17.8-20.1)*
LA/BW (mm/kg)	10.7 ± 0.95	12.4 ± 1.42*	13.5 ± 2.46*
LVM (g)	0.84 (0.76-0.91)	1.29 (1.17-1.43)*	1.27 (1.22-1.63)*
LVMI (g/kg)	1.57 (1.46-1.70)	2.32 (2.12-2.63)*	2.44 (2.31-3.08)*
RWT	0.35 ± 0.02	0.31 ± 0.02*	0.35 ± 0.04#
% area MI	No infarction	26.23 ± 5.77	27.62 ± 7.67

*Data are expressed as mean ± standard deviation or median and percentiles. MI-SED: sedentary myocardial infarction; MI-AE: aerobic exercise myocardial infarction; n: number of animals; HR: heart rate; LVDD and LVSD: left ventricular diastolic and systolic diameters respectively; DPWT: left ventricular diastolic posterior wall thickness; AO: aorta diameter; LA: left atrial diameter; BW: body weight; LVM: left ventricular mass; LVMI: left ventricular mass index; RWT: relative wall thickness. % area MI: percentage of myocardial infarcted area. ANOVA and Bonferroni or Kruskal-Wallis and Dunn's test; *p<0.05 vs Sham; #p<0.05 vs MI-SED.*

Morphometric study

Cardiomyocyte diameter was smaller in infarcted groups than in Sham (Figure 3).

Gene expression

Gene expression of NADPH oxidase subunits NOX2, NOX4, $p22^{phox}$, and $p47^{phox}$ did not differ between groups (Table 5).

Discussion

In this study, we evaluated the effects of aerobic physical exercise on functional capacity, cardiac remodeling and gene expression of NADPH oxidase subunits in small-sized MI rat hearts.

The rodent experimental MI model has been widely used to investigate the pathophysiology and treatment of cardiac remodeling and heart failure.[26,27] However, as a rat's coronary circulation anatomy is not uniform, coronary artery ligation leads to a wide range of infarct sizes, cardiac remodeling, and LV dysfunction.[22] Therefore, an essential feature of studies aimed to establish therapeutic strategies is to evaluate animals with comparable infarction sizes. Thus, echocardiographic assessment of MI size and cardiac injury degree before initiating therapeutic strategies should be mandatory.

Table 3 – Echocardiographic parameters of left ventricular systolic function

	SHAM (n=15)	MI-SED (n=10)	MI-AE (n=12)
EFS (%)	49.7 ± 3.40	27.0 ± 5.23*	26.6 ± 7.91*
PWSV (mm/s)	42.1 ± 5.66	35.9 ± 5.37	38.7 ± 9.28
FAC (%)	67.3 ± 5.07	41.1 ± 9.95*	37.6 ± 10.5*
Tei index	0.46 ± 0.06	0.58 ± 0.12*	0.58 ± 0.15*
S' average (cm/s)	3.55 ± 0.40	3.15 ± 0.34	3.20 ± 0.47

*Data are expressed as mean ± standard deviation. MI-SED: sedentary myocardial infarction; MI-AE: aerobic exercise myocardial infarction; n: number of animals; EFS: endocardial fractional shortening; PWSV: posterior wall shortening velocity; Tei index: myocardial performance index; S' average: mean maximum systolic displacement velocities for lateral and septal walls of the mitral annulus assessed by tissue Doppler imaging. ANOVA and Bonferroni; *p<0.05 vs Sham.*

Table 4 – Echocardiographic parameters of left ventricular diastolic function

	SHAM (n=15)	MI-SED (n=10)	MI-AE (n=12)
Mitral E (cm/s)	77.0 (71.0-85.0)	72.5 (69.3-79.5)	75.5 (72.8-78.0)
Mitral A (cm/s)	49.1 ± 12.2	54.3 ± 11.9	59.9 ± 16.8
E/A	1.71 (1.42-1.79)	1.32 (1.26-1.49)	1.23 (1.07-1.35)*
IVRT (m/s)	26.5 ± 3.42	29.7 ± 5.75	28.0 ± 3.79
E' average (cm/s)	4.20 ± 0.63	3.52 ± 0.62*	3.58 ± 0.50*
E' lateral (cm/s)	4.16 ± 0.73	3.20 ± 0.56*	3.24 ± 0.74*
E' septal (cm/s)	4.24 ± 0.61	3.84 ± 0.88	3.92 ± 0.79
E/E' average	19.1 ± 2.65	21.8 ± 3.47	21.6 ± 2.35
A' average (cm/s)	3.05 (2.65-3.90)	3.77 (2.96-4.85)	3.82 (2.81-4.04)
A' lateral (cm/s)	3.40 (2.80-3.80)	3.95 (3.17-4.85)	4.15 (3.27-4.55)
A' septal (cm/s)	3.25 ± 1.12	3.81 ± 1.21	3.11 ± 0.76
E'/A'	1.34 ± 0.39	0.95 ± 0.25*	1.05 ± 0.35

*Data are expressed as mean ± standard deviation or median and percentiles. MI-SED: sedentary myocardial infarction; MI-AE: aerobic exercise myocardial infarction; n: number of animals; Mitral E: peak velocity of early-diastolic mitral inflow; Mitral A: peak velocity of late-diastolic mitral inflow; IVRT: isovolumetric relaxation time; E': peak initial diastolic displacement velocity of the mitral annulus; A': peak late diastolic displacement velocity of the mitral annulus. ANOVA and Bonferroni or Kruskal-Wallis and Dunn's test; *p<0.05 vs Sham.*

We have previously observed that the minimum infarct size for inducing structural, functional, and clinical abnormalities was 36%, 38%, and 40% of the total LV area, respectively.[28] We therefore did not expect to find considerable cardiac changes by evaluating rats with MI sizes below 30%. However, this study showed that, at the end of the experimental period, infarcted groups presented increased LV diastolic and systolic diameter, left atrial diameter, and LV mass, with systolic dysfunction characterized by reduced endocardial fractional shortening and fractional area change, as well as increased Tei index. Except for reduced septal and average E' wave, the diastolic function did not differ between infarcted and Sham groups. Our data therefore showed that cardiac remodeling with left cardiac chambers dilation and LV systolic dysfunction can be well characterized in rats with small-sized infarction area.

The fact that body weight did not differ between groups reinforces the slight degree of myocardial injury. Cardiac cachexia is characterized by a significant reduction in body weight,[29,30] and can be found in post-infarction rats with large infarction areas.[22]

In this study, we used a moderate intensity aerobic exercise protocol adapted from previously published studies.[17] Maximum running velocity was established for each rat according to its functional capacity, evaluated by maximum effort test performed on a treadmill at the beginning and middle of the exercise protocol.[15] At the end of the experiment, we noted that exercise was safe and the MI-AE group attained a higher treadmill time and distance run than MI-SED and Sham groups. Aerobic exercise has long been shown to improve functional capacity in both animal and human heart failure.[31] The Sham rat results also underlined a reduced functional capacity caused by sedentary lifestyle.

Despite improving functional performance, the effects of aerobic exercise on cardiac remodeling were not substantial in small-sized MI rats. As a common finding in MI rats is a decrease in LV relative wall thickness,[22] we may conclude that exercise was helpful in preserving LV geometry, as the relationship between LV diastolic posterior wall thickness and LV diastolic diameter was reduced in MI-SED and preserved in the MI-AE group.

Among various MI-induced alterations, increased oxidative stress plays an important role in cardiac remodeling progression.[5]

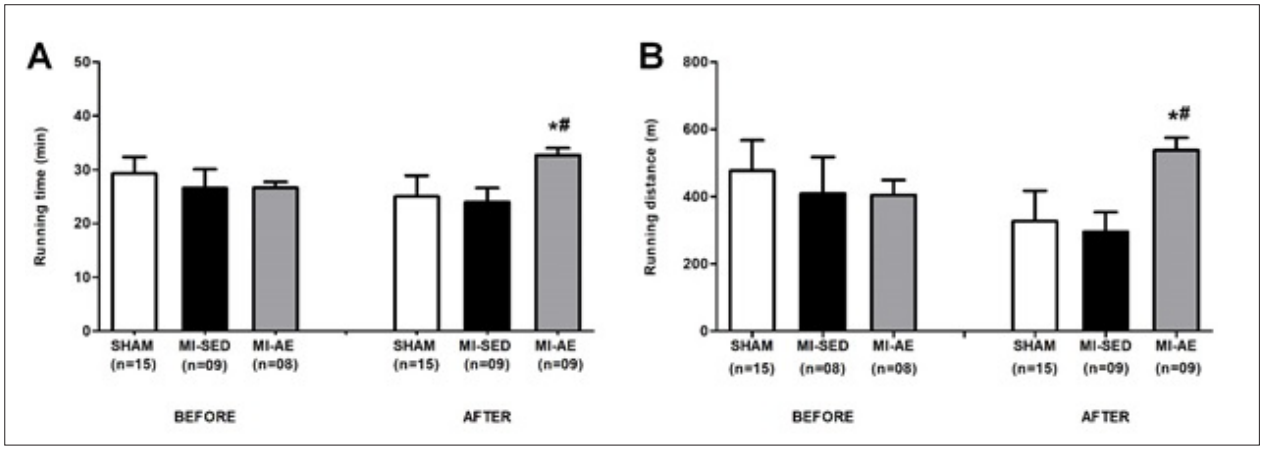


Figure 2 – *Functional capacity evaluated by maximal exercise test. Running time (A) before and after exercise; running distance (B) before and after exercise. MI-SED: sedentary myocardial infarction; MI-AE: aerobic exercise myocardial infarction; n: number of animals. Data are expressed as mean ± standard deviation; ANOVA and Bonferroni; *p<0.05 vs SHAM; #p<0.05 vs MI-SED.*

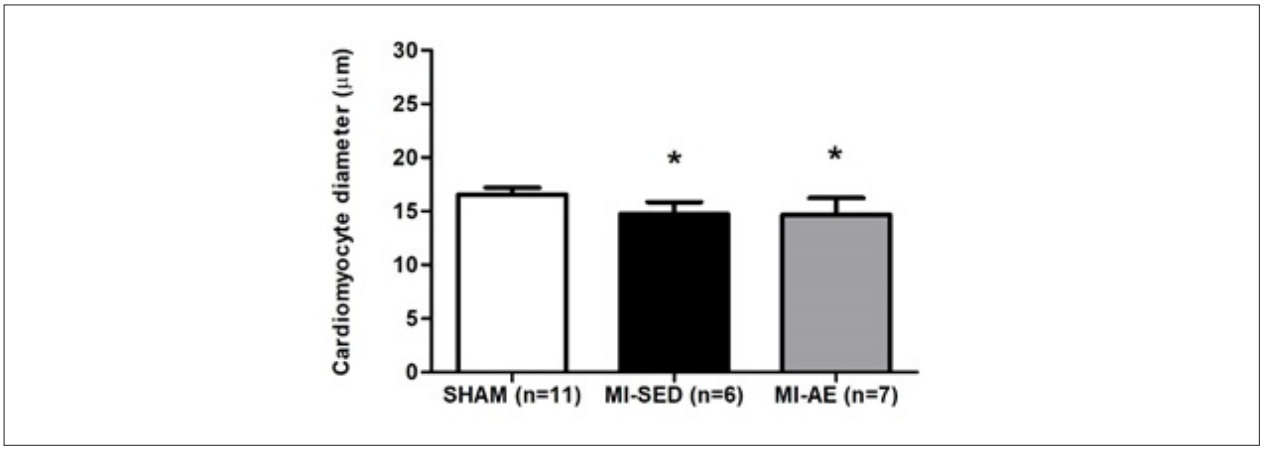


Figure 3 – *Cardiomyocyte diameters. MI-SED: sedentary myocardial infarction; MI-AE: aerobic exercise myocardial infarction; n: number of animals. Data are expressed as mean ± standard deviation; ANOVA and Bonferroni; *p<0.05 vs SHAM.*

Table 5 – Gene expression of NADPH oxidase complex subunits

Gene	SHAM (n=9)	MI-SED (n=5)	MI-AE (n=5)
Nox2	1.00 ± 0.56	0.83 ± 0.34	1.07 ± 0.26
Nox4	0.99 (0.62-1.20)	1.38 (0.60-1.95)	1.36 (0.79-1.40)
p22phox	1.00 ± 0.35	1.12 ± 0.51	1.16 ± 0.18
p47phox	1.00 ± 0.56	0.83 ± 0.34	1.07 ± 0.26

Data are expressed as mean ± standard deviation or median and percentiles. MI-SED: sedentary myocardial infarction; MI-AE: aerobic exercise myocardial infarction; n: number of animals; ANOVA and Bonferroni or Kruskal-Wallis and Dunn's test; p>0.05.

In this study, gene expression of NADPH oxidase complex subunits NOX2, NOX4, $p22^{phox}$, and $p47^{phox}$ did not differ between groups, which suggests that this important source of reactive oxygen species generation[4] was not involved in the cardiac remodeling observed in rats with small-sized infarction. Increased gene expression of NOX2 and NOX4 has been observed in large-sizes MI rodents.[32] One limitation of this study is that we have evaluated NADPH oxidase complex by analyzing the gene expression of its subunits. Therefore, additional studies are needed to assess the activity of the NADPH oxidase complex.

Since transition from compensated LV dysfunction to heart failure is mainly found in hearts with large transmural infarction,[22] most authors have evaluated the effects of exercise on hearts with large infarct sizes[8,10,33,34] and most studies have shown

favorable effects of aerobic exercise on MI-induced cardiac remodeling.[8,10,33] Only a few researchers have analyzed the cardiac effects of exercise in rats with small-sized MI.[35,36] By initiating exercise within four weeks post MI induction, these authors have observed beneficial cardiac effects of physical exercise.[35,36] In this study we showed for the first time that late aerobic exercise, initiated three months after MI, when cardiac remodeling is stable, attenuates cardiac geometry changes in rats with small-sized infarction. Our study therefore reinforces the concept of potential benefit from cardiac rehabilitation after acute coronary syndromes, regardless of cardiac injury degree.[37]

Conclusion

In conclusion, small-sized MI changes cardiac structures and the left ventricular systolic function. Late aerobic physical exercise improves functional capacity and attenuates left ventricular geometry change. NADPH oxidase subunits gene expression is not involved in cardiac remodeling nor is modulated by aerobic exercise in rats with small-sized MI.

Acknowledgements

We would like to thank Colin Edward Knaggs for the English editing. Financial support was provided by the National Council for Scientific and Technological Development (CNPq) (protocols 308557/2018-2 and 310876/2018-4); the São Paulo Research Foundation (FAPESP) (protocols 2014/21972 - 3 and 2014/00747-1); the Coordination for the Improvement of Higher Education Personnel (CAPES) (protocols 88882.432904/2019-01 and 153424/2018-4); and the Pro-Rectory of Post-Graduate Studies and Research (PROPe) at UNESP.

Author contributions

Conception and design of the research: Souza LM, Okoshi MP, Gomes MJ, Gatto M, Rodrigues EA, Pontes THD, Damatto FC, Oliveira LRS, Borim PA, Lima ARR, Zornoff LAM, Okoshi K, Pagan LU; Data acquisition: Souza LM, Gomes MJ, Gatto M, Rodrigues EA, Pontes THD, Damatto FC, Oliveira LRS, Borim PA, Lima ARR, Pagan LU; Analysis and interpretation of the data and Statistical analysis: Souza LM, Gomes MJ, Pagan LU; Obtaining financing and Writing of the manuscript: Souza LM, Okoshi MP, Gomes MJ, Pagan LU; Critical revision of the manuscript for intellectual content: Souza LM, Okoshi MP, Gomes MJ, Gatto M, Pagan LU.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by CNPq (Process number 308557/2018-2 and 310876/2018-4); FAPESP (Process number 2014/21972-3 and 2014/00747-1); CAPES (Process number 88882.432904/2019-01 and 153424/2018-4), and PROPe, UNESP.

Study Association

This article is part of the thesis of master submitted by Lidiane Moreira de Souza, from Programa de pós-graduação em Fisiopatologia em Clínica Médica na Faculdade Medicina de Botucatu - UNESP.

References

1. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation. 2019;139(10):e56-528.
2. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling - concepts and clinical implications: a consensus paper from an International Forum On Cardiac Remodeling. J Am Coll Cardiol. 2000;35(3):569-82.
3. Martinez PF, Bonomo C, Guizoni DM, Junior SA, Damatto RL, Cezar MD, et al. Modulation of MAPK and NF-kappaB signaling pathways by antioxidant therapy in skeletal muscle of heart failure rats. Cell Physiol Biochem. 2016;39(1):371-84.
4. Tsutsui H, Kinugawa S, Matsushima S. Oxidative stress and heart failure. Am J Physiol Heart Circ Physiol. 2011;301(6):H2181-90.
5. Octavia Y, Brunner-La Rocca HP, Moens AL. NADPH oxidase-dependent oxidative stress in the failing heart: From pathogenic roles to therapeutic approach. Free Radic Biol Med. 2012;52(2):291-7.
6. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey Jr. DE, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: executive summary: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. Circulation. 2013;128(16):1810-52.
7. Cai M, Wang Q, Liu Z, Jia D, Feng R, Tian Z. Effects of different types of exercise on skeletal muscle atrophy, antioxidant capacity and growth factors expression following myocardial infarction. Life Sci. 2018 Nov 15;213:40-9.
8. Guizoni DM, Oliveira-Junior SA, Noor SL, Pagan LU, Martinez PF, Lima AR, et al. Effects of late exercise on cardiac remodeling and myocardial calcium handling proteins in rats with moderate and large size myocardial infarction. Int J Cardiol. 2016 Oct 15;221:406-12.
9. Qin R, Murakoshi N, Xu D, Tajiri K, Feng D, Stujanna EN, et al. Exercise training reduces ventricular arrhythmias through restoring calcium handling and sympathetic tone in myocardial infarction mice. Physiol Rep. 2019;7(4):e13972.
10. Batista DF, Gonçalves AF, Rafacho BP, Santos PP, Minicucci MF, Azevedo PS, et al. Delayed rather than early exercise training attenuates ventricular remodeling after myocardial infarction. Int J Cardiol. 2013;170(1):e3-4.
11. Sharma NM, Liu X, Llewellyn TL, Katsurada K, Patel KP. Exercise training augments neuronal nitric oxide synthase dimerization in the paraventricular nucleus of rats with chronic heart failure. Nitric Oxide. 2019 Jun 1;87:73-82.
12. Xu X, Wan W, Garza MA, Zhang JQ. Post-myocardial infarction exercise training beneficially regulates thyroid hormone receptor isoforms. J Physiol Sci. 2018;68(6):743-8.
13. Martinez PF, Bonomo C, Guizoni DM, Oliveira Junior SA, Damatto RL, Cezar MD, et al. Influence of N-acetylcysteine on oxidative stress in slow-twitch soleus muscle of heart failure rats. Cell Physiol Biochem. 2015;35(1):148-59.
14. Lima ARR, Martinez PF, Damatto RL, Cezar MDM, Guizoni DM, Bonomo C, et al. Heart failure-induced diaphragm myopathy. Cell Physiol Biochem. 2014;34(2):333-45.
15. Pagan LU, Damatto RL, Cezar MD, Lima AR, Bonomo C, Campos DH, et al. Long-term low intensity physical exercise attenuates heart failure development in aging spontaneously hypertensive rats. Cell Physiol Biochem. 2015;36(1):61-74.

16. Gomes MJ, Martinez PF, Campos DHS, Pagan LU, Bonomo C, Lima AR, et al. Beneficial effects of physical exercise on functional capacity and skeletal muscle oxidative stress in rats with aortic stenosis-induced heart failure. Oxid Med Cell Longev. 2016 Jan 20;2016:8695716.

17. Moreira JB, Bechara LR, Bozi LH, Jannig PR, Monteiro AW, Dourado PM, et al. High- versus moderate-intensity aerobic exercise training effects on skeletal muscle of infarcted rats. J Appl Physiol. 2013;114(8):1029-41.

18. Okoshi K, Ribeiro HB, Okoshi MP, Matsubara BB, Gonçalves G, Barros R, et al. Improved systolic ventricular function with normal myocardial mechanics in compensated cardiac hypertrophy. Jpn Heart J. 2004;45(4):647-56.

19. Guimaraes JF, Muzio BP, Rosa CM, Nascimento AF, Sugizaki MM, Fernandes AA, et al. Rutin administration attenuates myocardial dysfunction in diabetic rats. Cardiovasc Diabetol. 2015 Jul 17;14:90.

20. Rosa CM, Gimenes R, Campos DH, Guirado GN, Gimenes C, Fernandes AA, et al. Apocynin influence on oxidative stress and cardiac remodeling of spontaneously hypertensive rats with diabetes mellitus. Cardiovasc Diabetol. 2016;15(1):126.

21. Cezar MD, Damatto RL, Pagan LU, Lima AR, Martinez PF, Bonomo C, et al. Early spironolactone treatment attenuates heart failure development by improving myocardial function and reducing fibrosis in spontaneously hypertensive rats. Cell Physiol Biochem. 2015;36(4):1453-66.

22. Martinez PF, Okoshi K, Zornoff LA, Oliveira SAJ, Campos DH, Lima AR, et al. Echocardiographic detection of congestive heart failure in postinfarction rats. J Appl Physiol. 2011;111(2):543-51.

23. Okoshi MP, Matsubara LS, Franco M, Cicogna AC, Matsubara BB. Myocyte necrosis is the basis for fibrosis in renovascular hypertensive rats. Braz J Med Biol Res. 1997;30(9):1135-44.

24. Gimenes C, Gimenes R, Rosa CM, Xavier NP, Campos DHS, Fernandes AAH, et al. Low intensity physical exercise attenuates cardiac remodeling and myocardial oxidative stress and dysfunction in diabetic rats. J Diabetes Res. 2015 Oct 5;2015:457848.

25. Cezar MD, Damatto RL, Martinez PF, Lima AR, Campos DH, Rosa CM, et al. Aldosterone blockade reduces mortality without changing cardiac remodeling in spontaneously hypertensive rats. Cell Physiol Biochem. 2013;32(5):1275-87.

26. Garza MA, Wason EA, Cruger JR, Chung E, Zhang JQ. Strength training attenuates post-infarct cardiac dysfunction and remodeling. J Physiol Sci. 2019;69(3):523-30.

27. Daliang Z, Lifang Y, Hong F, Lingling Z, Lin W, Dapeng L, et al. Netrin-1 plays a role in the effect of moderate exercise on myocardial fibrosis in rats. PLoS One. 2019;14(2):e0199802.

28. Minicucci MF, Azevedo PS, Martinez PF, Lima ARR, Bonomo C, Guizoni DM, et al. Critical infarct size to induce ventricular remodeling, cardiac dysfunction and heart failure in rats. Int J Cardiol. 2011;151(2):242-3.

29. Okoshi MP, Romeiro FG, Paiva SA, Okoshi K. Heart failure-induced cachexia. Arq Bras Cardiol. 2013;100(5):476-82.

30. Okoshi MP, Capalbo RV, Romeiro FG, Okoshi K. Cardiac cachexia: perspectives for prevention and treatment. Arq Bras Cardiol. 2017;108(1):74-80.

31. Cattadori G, Segurini C, Picozzi A, Padeletti L, Anza C. Exercise and heart failure: an update. ESC Heart Fail. 2018;5(2):222-32.

32. Looi YH, Grieve DJ, Siva A, Walker SJ, Anilkumar N, Cave AC, et al. Involvement of NOX2 NADPH oxidase in adverse cardiac remodeling after myocardial infarction. Hypertension. 2008;51(2):319-25.

33. Barcelos GT, Rossato DD, Perini JL, Pinheiro LP, Carvalho C, Jaenisch RB, et al. Effects of l-arginine supplementation associated with continuous or interval aerobic training on chronic heart failure rats. Metabolism. 2017 Nov;76:1-10.

34. Teixeira RB, Zimmer A, Castro AL, Carraro CC, Casali KR, Dias IGM, et al. Exercise training versus T3 and T4 hormones treatment: the differential benefits of thyroid hormones on the parasympathetic drive of infarcted rats. Life Sci. 2018 Mar 1;196:93-101.

35. Almeida SA, Claudio ERG, Mengal V, Brasil GA, Merlo E, Podratz PL, et al. Estrogen therapy worsens cardiac function and remodeling and reverses the effects of exercise training after myocardial infarction in ovariectomized female rats. Front Physiol. 2018 Sep 5;9:1242.

36. Campos JC, Queliconi BB, Bozi LHM, Bechara LRG, Dourado PMM, Andres AM, et al. Exercise reestablishes autophagic flux and mitochondrial quality control in heart failure. Autophagy. 2017;13(8):1304-17.

37. Aragam KG, Dai D, Neely ML, Bhatt DL, Roe MT, Rumsfeld JS, et al. Gaps in referral to cardiac rehabilitation of patients undergoing percutaneous coronary intervention in the United States. J Am Coll Cardiol. 2015;65(19):2079-88.

The Importance of Post-Infarction Exercise Programs

José Antônio Caldas Teixeira[1,2]

Universidade Federal Fluminense - Medicina Clínica,[1] *Niterói, RJ - Brazil*

Fit Labor Centro de Performance Humana,[2] *Niterói, RJ - Brazil*

Short Editorial related to the article: Effects of Late Aerobic Exercise on Cardiac Remodeling of Rats with Small-Sized Myocardial Infarction

Physical activity and exercising are said to reduce the risk of cardiovascular mortality in the general population by 30%–50%, and mortality from any cause by 20%–50%.[1] In cardiac patients, for each 1 Met increment (3.5 mL O_2 kg^{-1} min^{-1}) in functional capacity (FC) obtained in a cardiac rehabilitation program (CRP), we have a reduction in overall mortality of up to 13%.[1,2] They reduce global hospitalization by 18%, and improve quality of life (QoL) in this population.[2,3] After an angioplasty, CRP results in a 20% reduction in cardiac events and in the number of hospitalizations compared to individuals who remained sedentary.[1,2,4]

In this context, CRPs have established themselves as a safe therapeutic strategy, which mitigates the effects of progressive physical deconditioning resulting from cardiovascular diseases (CD). Well-oriented exercise is the cornerstone in handling CD and its main risk factors.[1-6] CRPs, especially in post-acute coronary syndrome (ACS) and patients with ventricular dysfunction, bring important benefits of clinical impact, with an evidence level IA in this population, referenced by numerous consensuses, meta analyses and guidelines.[1-4,6,7]

The importance of starting a CRP, with an emphasis on aerobic training (AT), right after the stabilization of an ACS (acute coronary syndrome), is reviewed in different articles and meta analyses.[1-3,6-8] AT is associated with a lower expression of beta-adrenergic receptors, which predict prognosis in patients with a larger infarcted area. It improves several variables related to prognosis and FC, in addition to echocardiographic parameters (ECHO) of ventricular remodeling, and biomarkers.[8,9,10]

The literature mentions numerous beneficial effects, not only systemic, but mainly cardioprotective effects.[1-4,6,8,11] Précoma et al.[3] and Fletcher et al.[4] list these effects, but here we will highlight one of the hemodynamics: cardiac remodeling.

Acute myocardial infarction (AMI) can induce changes in ventricular geometry, leading to adverse ventricular remodeling.[8-10,12] This change in ventricular geometry is the main contributor to the future development of ventricular dysfunction, despite advances in revascularization and drug therapies.[9] Left ventricular (LV) remodeling is an accurate predictor of cardiac mortality after AMI,[8-10,12] but it is not clear how exercise affects this process. Haykowsky et al.,[9] in their meta-analysis, analyze this effect, showing different results. They have found that, although the beneficial effects on ventricular remodeling exist, they are based on population characteristics, modality, and variation in the prescription of exercises and interventions, and it is not possible to define why these variations occur.

Understanding these inconsistencies and the effects of exercise on LV remodeling is important, as this knowledge can be used to increase the benefits of exercise after AMI.

An article by Souza et al.[13] analyzes the late effects of AT in late post-infarction in animal models. This represents yet another attempt to clarify this issue.

In an elegant, controlled study, Souza et al.[13] induced myocardial infarction (MI) by ligating the left anterior descending coronary artery. Three months later, surviving rats were subjected to transthoracic ECHO and exercise testing, then were assigned to three groups: sham-operated animals were used as controls (Sham n=15); sedentary MI (MI-SED, n=22) and aerobic exercised MI (MI-AE, n=21) for three months. They evaluated the influence of AE on FC, cardiac structures, LV function, and NADPH (nicotinamide adenine dinucleotide phosphate) oxidase subunit gene expression in rats with small-sized MI.

The authors used a moderate intensity AE protocol. They observed that exercise was safe, and the MI-AE group attained a higher treadmill time and distance run than the MI-SED and Sham-operated groups. The sham surgery results included reduced FC caused by a sedentary lifestyle. Despite improving functional performance, the effects of AE on cardiac remodeling were not substantial in small-sized myocardial infarction rats. But AE was helpful in preserving LV geometry, as the relationship between LV diastolic posterior wall thickness and LV diastolic diameter was reduced in the MI-SED group and preserved in the MI-AE group. The NADPH oxidase subunit gene expression, an important source of reactive oxygen species generation, was not involved in the cardiac remodeling observed in rats with small-sized infarction.

For the first time, the study shows that late AE, initiated three months after MI, when cardiac remodeling is stable, attenuates cardiac geometry changes in rats with small-sized infarction. The authors reinforce the concept of the potential benefit from cardiac rehabilitation after ACS regardless of the degree of cardiac injury.

Keywords

Myocardial Infarction/mortality; Exercise; Cardiac, Rehabilitation; Physical Activity; Rats; Ventricular Dysfunction; Echocardiography/methods.

Mailing Address: José Antônio Caldas Teixeira •
Universidade Federal Fluminense - Medicina Clínica - Avenida Marquês do Paraná, 303. Postal Code 24070-035, Niterói, RJ – Brazil
E-mail: jacaldas_@hotmail.com

DOI: hhttps://doi.org/10.36660/abc.20210109

References

1. Franklin BA, Thompson PT, Al-Zaiti SS, Albert CM, Hivert MF, Levine BD, Lobelo F et al. On behalf of the American Heart Association Physical Activity Committee of the Council on Lifestyle and Cardiometabolic Health; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Stroke Council. Exercise-Related Acute Cardiovascular Events and Potential Deleterious Adaptations Following Long-Term Exercise Training: Placing the Risks Into Perspective–An Update. Circulation. 2020; 141(13):E705-E736.
2. Carvalho T, Milani M, Ferraz AS, Silveira AD, Herdy AH, Hossri CAC, et al. Diretriz Brasileira de Reabilitação Cardiovascular – 2020. Arq Bras Cardiol. 2020; 114(5):943-87.
3. Précoma DB, Oliveira GMM, Simão AF, Dutra OP, Coelho OR, Izar MCO, et al. Updated Cardiovascular Prevention Guideline of the Brazilian Society of Cardiology – 2019. Arq Bras Cardiol. 2019;113(4):787-891.
4. Fletcher GF, Landolfo C, Niebauer J Ozemek C, Arena R, Lavie C. Promoting Physical Activity and Exercise. JACC Health Promotion Series. J Am Coll Cardiol. 2018;72(14):1622-39.
5. WORLD Health Organization (WHO). guidelines on physical activity and sedentary behaviour. Geneva; 2020. [Licence: CC BY-NC-SA 3.0 IGO.]
6. Hansen D, Niebauer J, Cornelissem V, Barna O, Neunhaüsere D, Settler C, et al. Exercise Prescription in Patients with Different Combinations of Cardiovascular Disease Risk Factors: A Consensus Statement from the EXPERT Working Group. Sports Med. https://doi.org/10.1007/s40279-018-0930-4. Published online: 04 May 2018.
7. Jayo-Montoya JA, Maldonado-Martin, S, Aispuru GR, Gorotegi-Anduaga I, Gallardo T, Matajira-Chia T, et al. Low-Volume High-Intensity Aerobic Interval Training Is an Efficient Method to Improve Cardiorespiratory Fitness After Myocardial Infarction PILOT STUDY FROM THE INTERFARCT PROJECT.J Cardiopulm Rehabil Prev. 2020;40(1):48-54.
8. Haykowsky M, Scott J, Esch B, Schopflocher D, Miers J, Paterson I, Warburton D. et al. A meta-analysis of the effects of exercise training on left ventricular remodeling following myocardial infarction: start early ando go longer for greatest exercise benefits on remodeling. Trials. 201 Apr 04;12:92.
9. Trachse LD, David LP, Gayda M, Henri C, Hayami D, Thorin-Trescases N, Thorin E et al. The impact of high-intensity interval training on ventricular remodeling in patients with a recent acute myocardial infarction – A randomized training intervention pilot study. Clin Cardiol. 2019; 42(12):1222-31.
10. Garza MA, Wason EA, Zhang JQ. Cardiac remodeling and physical training post myocardial infarction. World J Cardiol. 2015; 7(2): 52-64.
11. Thijssen DHJ, Redington A, KP, Hopman MTE; Jones H. Association of Exercise Preconditioning With Immediate Cardioprotection: A Review. JAMA Cardiol. 2018;3(2):169-76.
12. Sakuragi S, Shuichitakagi, Suzuki S, Sakamaki F, Hiroshitakaki, Naohikoaihara, Yoshioyasumura, Yoichigoto. Patients with Large Myocardial Infarction Gain a Greater Improvement in Exercise Capacity after Exercise Training than Those with Small to Medium Infarction. Clin. Cardiol. 2003; 26(6):280-6.
13. Souza LM, Okoshi MP, Gomes MJ, Gatto M, Rodrigues EA, Pontes THD, Damatto FC, et al. Effects of late aerobic exercice on cadiac remodeling of rats with small myocardial infarction. artigo ABC-2019-0813

Original Article

Visceral Obesity and High Systolic Blood Pressure as the Substrate of Endothelial Dysfunction in Obese Adolescents

Maria Fernanda Hussid,[1] Felipe Xerez Cepeda,[1] Camila P. Jordão,[2] Rafaela R. P. Lopes-Vicente,[1] Leslie Virmondes,[1] Keyla Y. Katayama,[1] Ezequiel F. de Oliveira,[1] Luis V. F. Oliveira,[3] Fernanda Marciano Consolim-Colombo,[1,2] Ivani Credidio Trombetta[1,2]

Universidade Nove de Julho (UNINOVE),[1] São Paulo, SP - Brazil
Instituto do Coração (InCor), Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo,[2] São Paulo, SP - Brazil
Centro Universitário de Anápolis (UniEvangélica),[3] Anápolis, GO - Brazil

Abstract

Background: **Obesity affects adolescence and may lead to metabolic syndrome (MetS) and endothelial dysfunction, an early marker of cardiovascular risk. Albeit obesity is strongly associated with obstructive sleep apnea (OSA), it is not clear the role of OSA in endothelial function in adolescents with obesity.**

Objective: **To investigate whether obesity during adolescence leads to MetS and/or OSA; and causes endothelial dysfunction. In addition, we studied the possible association of MetS risk factors and apnea hypopnea index (AHI) with endothelial dysfunction.**

Methods: **We studied 20 sedentary obese adolescents (OA; 14.2±1.6 years, 100.9±20.3kg), and 10 normal-weight adolescents (NWA, 15.2±1.2 years, 54.4±5.3kg) paired for sex. We assessed MetS risk factors (International Diabetes Federation criteria), vascular function (Flow-Mediated Dilation, FMD), functional capacity (VO_2peak) and the presence of OSA (AHI>1event/h, by polysomnography). We considered statistically significant a P<0.05.**

Results: **OA presented *higher waist* (WC), body fat, triglycerides, systolic (SBP) and diastolic blood pressure (DBP), LDL-c and lower HDL-c and VO_2peak than NWA. MetS was presented in the 35% of OA, whereas OSA was present in 86.6% of OA and 50% of EA. There was no difference between groups in the AHI. The OA had lower FMD than NWA (6.17±2.72 vs. 9.37±2.20%, p=0.005). There was an association between FMD and WC (R=-0.506, p=0.008) and FMD and SBP (R=-0.493, p=0.006).**

Conclusion: **In adolescents, obesity was associates with MetS and caused endothelial dysfunction. Increased WC and SBP could be involved in this alteration. OSA was observed in most adolescents, regardless of obesity. (Arq Bras Cardiol. 2021; 116(4):795-803)**

Keywords: **Adolescent; Obesity; Metabolic Syndrome; Hypertension; Diabetes; Waist Circumference; Sleep Apnea Obstructive; Endothelium; Risk Factors.**

Introduction

Obesity has been increasing rapidly worldwide and is considered a risk factor for chronic noncommunicable diseases. Children and adolescents have been seriously impacted by this trend, particularly in developing countries, according to the World Health Organization (WHO).[1] When assessing the nutritional status of school children aged 13 to 17 years, using the body mass index (BMI) for age, it was found that 23.7% of the male population is overweight, and 8.3% are obese.[2] The concern about the increased prevalence of obesity in the children and adolescents lies in the fact that it may be a predictor of adult obesity, leading to increased risk of chronic diseases such as type 2 diabetes, metabolic syndrome (MetS) and cardiovascular diseases (CVD).[3]

Indeed, it is clear in the literature that obesity is positively associated with incident MetS.[4] Studies carried in pubertal adolescents have demonstrated a prevalence of MetS ranging from 25 to 30%.[5] In this study they found that waist circumference (WC) was a predictor of MetS, and an 11% increase in the risk of MetS was detected for each 1 cm added to abdominal circumference.[5]

It is well established that the earliest marker of atherosclerosis is endothelial dysfunction,[6] which may be found in both hypertension and atherosclerosis. Endothelial dysfunction is also involved in physiological and pathological processes, including inflammation, insulin resistance and obesity, among other disorders.[6]

Flow-mediated dilation (FMD) by ultrasonography is a widely used noninvasive method to assess endothelium function, which may be a predictor of cardiovascular events in both asymptomatic and established cardiovascular disease (CVD) subjects. A change in FMD may be of prognostic value in humans.[7]

Mailing Address: Ivani Credidio Trombetta •
Universidade Nove de Julho (UNINOVE) - Rua Vergueiro, 235/249.
Postal Code 01504-001, São Paulo, SP – Brazil
E-mail: ivani.trombetta@gmail.com
Manuscript received August 12, 2019, revised manuscript November 11, 2019, accepted December 27, 2019

DOI: https://doi.org/10.36660/abc.20190541

Respiratory sleep disorders are among the many consequences of obesity, including obstructive sleep apnea syndrome (OSA). OSA is the most common sleep-disordered breathing syndrome, with a prevalence of 1 to 4% in childhood, which peaks at the 2 - 8year-old age group.[8] In children with obesity this percentage may reach 36%.[9] OSA has been correlated with obesity, providing a mild and chronic inflammatory environment. Patients with OSA experience hypoxic episodes and recurrent arousals during sleep due to increased sympathetic nervous system activity.[9] Trombetta et al.[10] have found that MetS and OSA patients had higher blood pressure (BP) levels than those with MetS without OSA. Increased sympathetic activity and impairment of baroreflex control were observed in these patients with OSA associated with MetS.[10] The association of obesity with OSA could increase the risk of endothelial dysfunction.[11]

In the present study, obese adolescents were compared with normal-weight adolescents regarding anthropometry, body composition, biochemical parameters, vascular reactivity, and sleep apnea. Our purpose was to investigate whether obesity during adolescence: 1) leads to MetS and/or OSA; and 2) causes endothelial dysfunction. In addition, we studied the possible association of MetS risk factors or apnea hypopnea index (AHI) with endothelial dysfunction.

Methods

Ethics Committee

The study was approved by the Research Ethics Committee of the Nove de Julho University (UNINOVE) under number 973.013, CAAE: 41899215.0.0000.5511. The adolescents' parents or guardians were informed about the study procedures performed and gave written informed consent. The adolescents were also informed about all the procedures performed and provided written assent.

Subjects

This was a cross-sectional study. Adolescents aged between 12 to 17 years, attending the Adolescent Outpatient Clinic of Universidade Nove de Julho (UNINOVE), were invited to participate in the study according to inclusion/exclusion criteria. Were included in the study post-pubertal adolescents according to Tanner staging (M4 girls or menarche and G4 boys),[12,13] normal-weight or obese according to WHO BMI classification (over two standard deviations for obesity) for boys and girls, physically inactive, and not under dietary or drug treatment for obesity, with or without MetS. Exclusion criteria were adolescents who were not at the post-pubertal stage, overweight, and those overweight and with suspected or confirmed genetic syndromes or neuroendocrinological disorders such as uncontrolled hypothyroidism and type 1 diabetes. Patients with eating disorder (anorexia nervosa, bulimia nervosa, or unspecified eating disorder) were also excluded. A total of 20 obese adolescents (OA) and 10 normal-weight adolescents (NWA) were studied.

The International Diabetes Federation (IDF) criteria were used for diagnosis of MetS. Central obesity was defined as WC ≥94cm for men and ≥80 cm for women, plus two of these four diagnostic criteria: (1) high-density lipoprotein cholesterol (HDL-c) <40 mg/dL (<1.03 mmol/L) in men and <50 mg/dL (<1.29 mmol/L) in women; (2) fasting glucose level ≥l00 mg/dL (≥5.6 mmol/L); (3) fasting triglyceride level (TG) ≥150 mg/dL (>1.69 mmol/L); and (4) systolic blood pressure (SBP) ≥130 mmHg and diastolic blood pressure (DBP) ≥ 85 mmHg.[14,15]

Measures

Anthropometric Measurements and Body Composition

Weight and height were assessed, and body mass index (BMI) was calculated. BMI was expressed as standard deviation scores (Z-score); normal weight was defined as a z-score between -2 and +1; overweight was defined as a z-score between +1 and +2; and obesity >+2. Assessment of body composition was performed by bioelectrical impedance analysis (RJL, Quantum II model, Clinton Twp, Mi, USA). WC and neck circumference (NC) were measured as previously described.[16,17]

Blood Pressure

SBP and DBP were measured with appropriate cuff size.[18-20]

Serum Analysis

Blood samples were collected after a 12-hour overnight fast. Concentrations of glucose, TG, total cholesterol, HDL-c, low density lipoprotein-cholesterol (LDL-c), TG/HDL-c ratio and LDL-c/HDL-c ratio were determined.

Nocturnal Polysomnography

A whole-night polysomnography (standard monitoring - level 1) was performed using an ambulatory sleep analysis system (Embla Somnologica Studio - EMBLA A10, version 3.1.2.; Flagahf Medical Devices, Iceland), as previously described.[21,22] As there were 12-year-old adolescents in the study, we used the American Academy of Sleep Medicine (AASM) criteria for OSA classification for children.[23] The OSA was defined as an AHI >1 event/hour; an AHI ≥1-4.99 was considered mild OSA; an AHI of 5-9.99 was considered moderate OSA; and AHI ≥10 severe OSA.[9]

In children an apnea is scored when peak signal excursions drop by ≥ 90% of pre-event baseline. Hypoventilation is scored when the arterial CO_2 (or surrogate) is > 50 mm Hg for > 25% of total sleep time. The AHI was calculated as the total number of respiratory events (apneas plus hypopneas) per hour of sleep. The arousal index was defined as the average number of arousals per hour of sleep. Oxygen desaturation (SaO_2 nadir) was defined as the lowest hemoglobin oxygen saturation recorded by pulse oximetry.[23]

Cardiopulmonary Exercise Testing (CPET)

CPET was performed on a treadmill, connected to a system composed of a gas analysis module, coupled to a flow module / wave analyzer in a breath-by-breath mode (BreezeCardiO2 System microcomputer; Medical Graphics Corporation-MGC, St. Paul, Mo, USA) and using a ramp protocol. The CPET allow to measure the functional capacity (VO_2peak) as maximum VO_2 attained at the end of the test.[24,25]

Reactive Hyperemia

Flow-Mediated Dilation (FMD)

FMD was performed with high-resolution vascular ultrasound (Vivid i, GE Medical Systems, Tirat Carmel, Israel), by measuring the vessel dilation (endothelium-dependent dilation) of the brachial artery, as previously described.[26] Briefly, subjects lay at rest for at least 10 minutes and a first resting scan was recorded. Then, an increased flow was induced by inflation of a sphygmomanometer cuff, located distally to the brachial artery in the forearm, to supra-systolic pressure (about 20 to 30 mmHg) for 5 minutes. The cuff was emptied and the flow and dilatation of the vessel, provided by the shear stress, was recorded. The difference between the basal diameter and the diameter after dilation was evaluated.

Reactive Hyperemia Index (RHI) by Peripheral Arterial Tonometry

Endothelial function was assessed by measuring the RHI by peripheral arterial tonometry (Endo-PAT2000; Itamar Medical, Caesarea, Israel) as previously described.[27] This method evaluates microvascular endothelial function.[28]

For assessment of both FMD and RHI, adolescents were instructed to fast for 4 to 6 hours, and to refrain from caffeine, chocolate, fatty foods, and exercise on the day of the examination.

Statistical Analysis

Statistical analysis was performed using the SPSS 20 Statistics program (IBM Corp., Armonk, NY, USA). The sample size was calculated using the website http://www.openepi.com. We took into account an 80% power, with a type 1 two-tailed error of 0.05. We used endothelial function variables (RHI and FMD) as the primary outcome. We chose the largest number of subjects, 30 adolescents for the study. Normality of the samples was tested by the Kolmogorov - Smirnov test. The parametric variables were expressed as mean ± standard deviation (SD) and nonparametric variables were expressed in median and interquartile range. The categorical data were described in absolute value and percentage of the total sample. The parametric variables of the OA and NWA groups were compared by independent Student's t-test while the non-parametric variables were compared by the Mann-Whitney test. Categorical variables were analyzed using the chi-square test and Pearson's correlation was used to analyze the correlation between variables of risk factors such as WC and BP and percentage of FMD. Probability values of $P<0.05$ were considered statistically significant.

Results

We initially recruited 56 adolescents; 26 of them were excluded – nine of them were Tanner scale I, II or III; five were overweight; five had endocrine disorders; one used medication and six declined to participate in the study. Our final sample was composed by 30 adolescents. Thus, we studied 20 OA (10 male) and 10 NWA (5 male) (Figure 1). Seven adolescents of the OA group had MetS (35%) and no NWA had MetS (Figure 2).

In Table 1, we describe the anthropometric and body composition measurements. Both groups were similar in sex distribution and height. As expected, OA had higher weight, BMI, NC and WC.

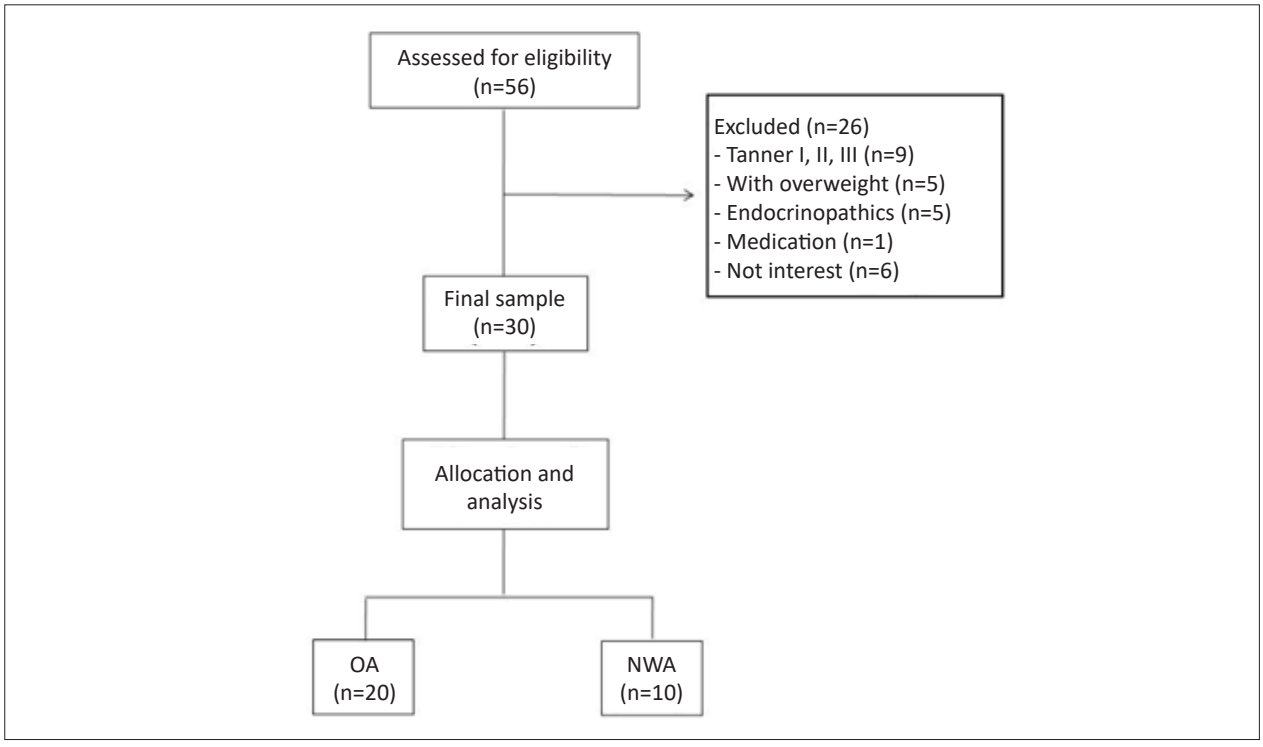


Figure 1 – *Flowchart of patient recruitment; OA: obese adolescents; NWA normal-weight adolescents.*

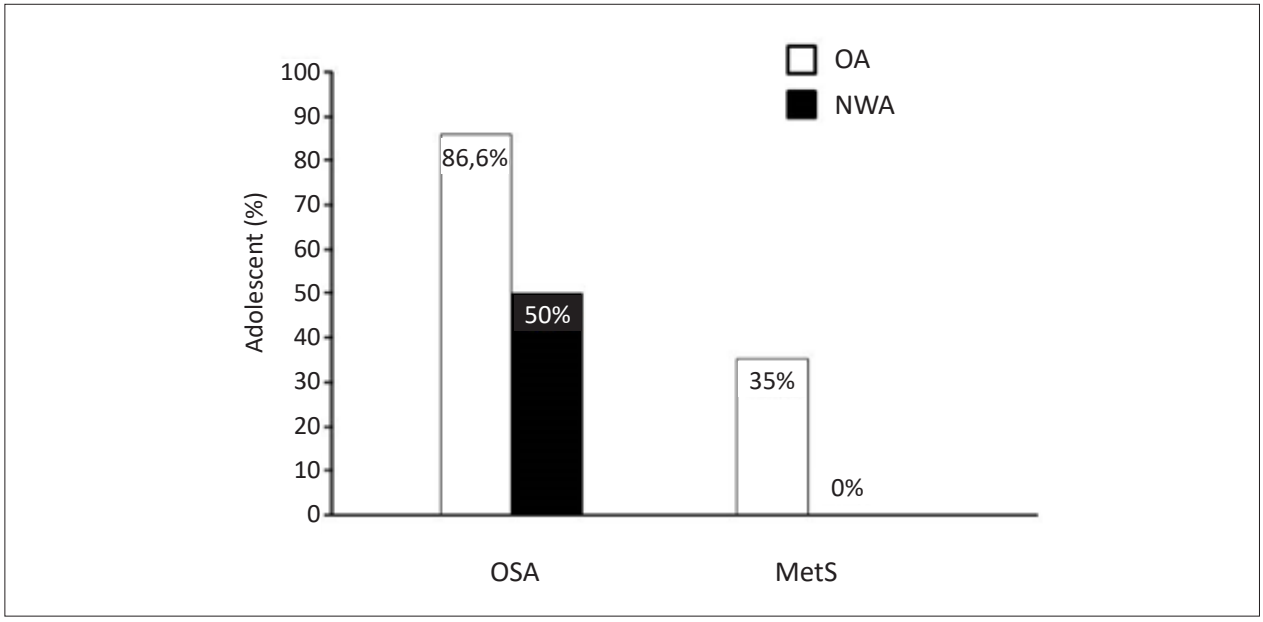


Figure 2 – *The percentage of obstructive sleep apnea (OSA) and metabolic syndrome (MetS) in adolescents with obesity (OA) and normal-weight (NWA).*

Table 1 – Anthropometric and body composition measurements of obese and normal-weight adolescents

	OA (n=20)	NWA (n=10)	p
Sex (M/F)	10/10	5/5	1
Age (yrs)	14.2±1.6	15.2±1.2	0.075
Weight (kg)	100.1±20.3	54.4±5.3	<0.001
Height (m)	1.67±0.08	1.65±0.6	0.760
BMI (kg/m²)	35.9±6.2	19.9±1.8	<0.001
NC (cm)	38.3±3.6	31.9±1.8	<0.001
WC (cm)	107.9 [100-114.5]	67.5 [66.4-73.7]	<0.001
Body water (%)	45.4±3.8	56.5±4.6	<0.001
Fat body mass (%)	38±5.2	22.9±6.3	<0.001
Lean body mass (%)	62±5.2	77.1±6.3	<0.001

Parametric data presented as mean ± standard deviation. Non-parametric data presented as median and interquartile range. OA: obese adolescents; NWA: normal-weight adolescents; BMI: body mass index; NC: neck circumference; WC: waist circumference.

Regarding body composition, there was a lower percentage of body water and lean body mass and higher fat body mass in OA.

Data on cardiovascular risk factors in the OA and NWA groups are shown in Table 2. There were no differences in HDL-c or glycaemia between the groups. Compared with NWA, OA had higher SBP and DBP levels, as well as higher levels of TG, LDL-c, TG/HDL-c ratio, non-HDL, LDL/HDL-c ratio, and total cholesterol. In CPET, the OA group showed lower VO_2peak compared to NWA. Results of polysomnography revealed that lower minimum O_2 in OA compared with NWA. No differences in arousal index and AHI were found between groups (Table 2). However, most OA (86.6%) and 50% of NWA had AHI ≥ 1 event/h (Figure 2).

In Figure 3, we present the prevalence of MetS risk factors according to the IDF.[15] In Figure 4 - panel A, we showed the FMD analyses. In one participant of the OA group, bifurcation of the brachial artery was detected, and we decided to exclude this record from the analysis. The analyses of the FMD showed that OA had lower vascular reactivity of large arteries compared to NWA (6.17±2.72% vs. 9.37±2.20%, p=0.005). Given this,

Table 2 – Cardiovascular risk factors in obese and normal-weight adolescents

	OA (n=20)	NWA (n=10)	p
SBP (mmHg)	120 [110-127.5]	110 [100-110]	0.001
DBP (mmHg)	75 [70-80]	65 [60-70]	0.005
Glycaemia (mg/mL)	84.9±5.4	89.3 ±7.2	0.140
TG (mg/dL)	120.5±48.3	71.1±28.8	0.020
HDL-c (mg/dL)	41.2±7.7	48.4 ±10.7	0.079
TG/HDL-c ratio	3.1±1.6	1.6±1	0.011
LDL-c (mg/dL)	97.5±25.7	69.9±22.2	0.015
nHDL-c (mg/dL)	121.5±27.5	83.2±26.2	0.004
LDL/HDL-c radio	2.4±0.8	2.6±0.7	0.007
Total cholesterol (mg/dL)	162.7±28.7	132.5±24.1	0.016
Nocturnal polysomnography			
AHI (events/h)	5.6±3.8	3.1±3.4	0.121
Minimum O_2 Sat (%)	90 [81-90]	92.5 [88.5-93]	0.026
Arousal index	50.6±18.1	50±9.3	0.943
Cardiopulmonary exercise testing			
VO_2peak (mL/kg/min)	30.6±7.7	23.4±5.9	0.022

Parametric data expressed as mean ± SD. Non-parametric data expressed as median and interquartile range. OA: obese adolescents; NWA: normal-weight adolescents; SBP: systolic blood pressure; DBP: diastolic blood pressure; TG: triglycerides; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

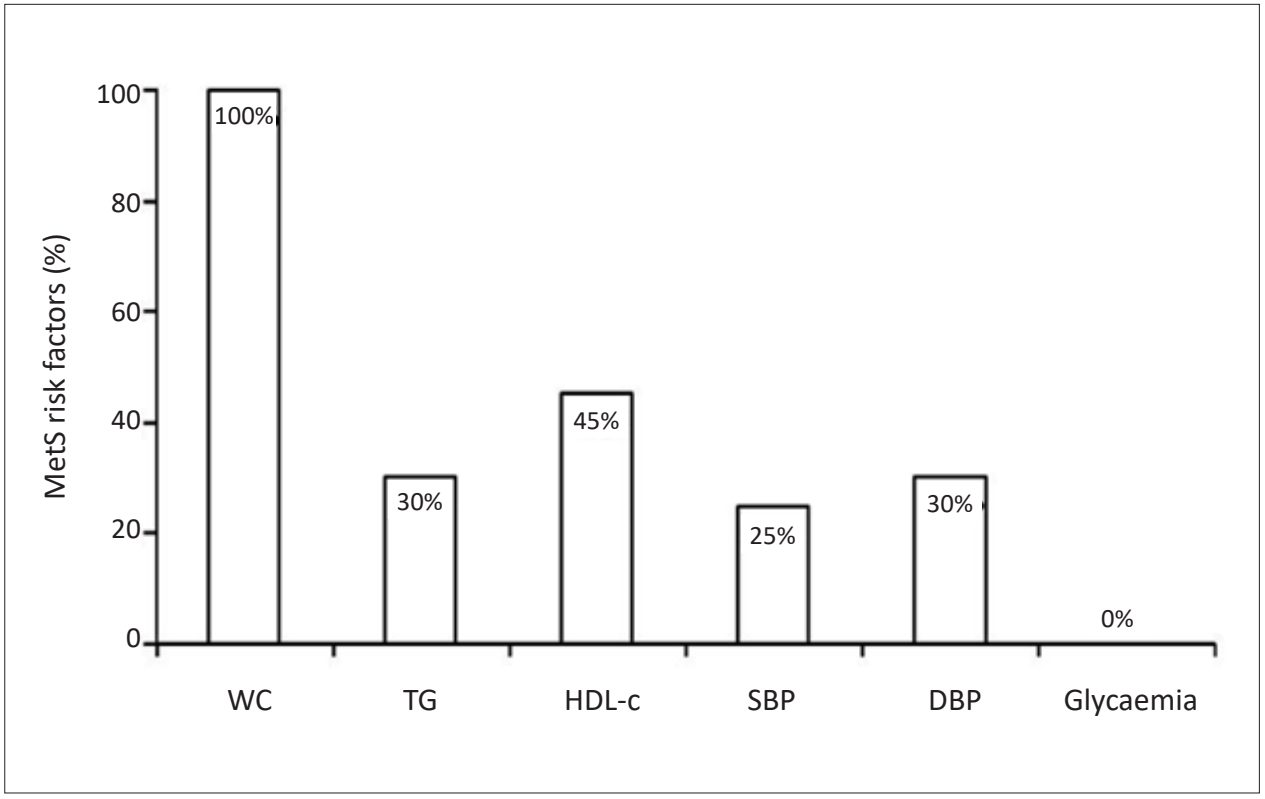


Figure 3 – *Percentage of risk factors for metabolic syndrome (MetS) in adolescent with obesity; WC: waist circumference; TG: triglycerides; HDL: high-density lipoprotein; SBP: systolic blood pressure; DBP: diastolic blood pressure.*

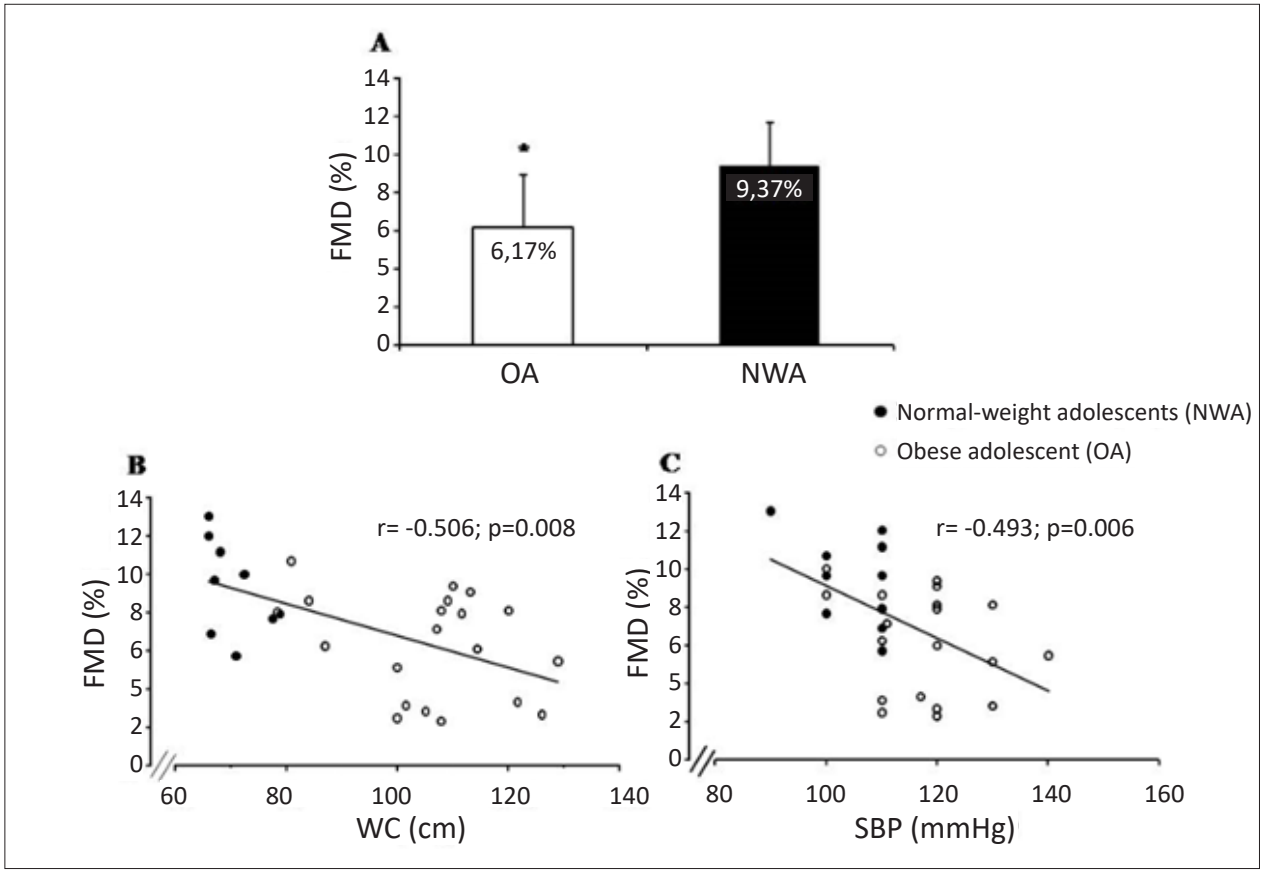


Figure 4 – *Reactive hyperemia by flow-mediated dilation (FMD) (Panel A); correlation coefficient between FMD and waist circumference (WC) (Panel B); correlation coefficient between FMD and systolic blood pressure (SBP) in obese adolescents (OA) and normal-weight adolescents (NWA) (Panel C). * p<0.005.*

we further explored the association between FMD with the risk factors for MetS, and found an associated between WC and FMD (R=-0.506, p=0.008; Figure 4 - panel B), and between SBP and FMD (R=-0.493, p=0.006; Figure 4 - panel C).

Discussion

The main finding of the present study is that OA have endothelial dysfunction, indicated by a decreased vascular reactivity. Moreover, based on correlation analyses, we can suggest that the WC and the SBP levels can be predictors of this dysfunction.

Obesity and MetS increase the risk of endothelial dysfunction, and OSA contributes to this worsening. However, despite the high prevalence of OSA in OA, there were no differences in the presence of OSA and the AHI between the groups studied. We can suggest that in adolescents other factors besides obesity, such as allergic rhinitis, asthma, and adenotonsillar hypertrophy, may contribute to the OSA. These findings have been found in other studies.[29] Therefore, in our study, impaired FMD was not associated with OSA, and the presence of OSA could not be attributed to obesity or MetS. We speculate that MetS potentiated endothelial dysfunction in the obese group, since 35% of obese patients in our sample had MetS.

Atherosclerosis and clinical manifestations of CVD have their origin in childhood,[30] and their early detection is very important for its prevention. Endothelial dysfunction is considered an early sign of atherosclerosis in children with CVD risk factors, and can be reversed by interventions to decrease cardiovascular risk.[30]

FMD with reactive hyperemia is a non-invasive method that evaluates nitric oxide (NO)-mediated endothelium-dependent vasodilation and is a suitable diagnostic method for the age group studied.[31] A meta-analysis identified that a 1% increase in FMD increases the future risk of cardiovascular events by 13%.[3] There is evidence that obese children and adolescents have lower vascular compliance and distensibility than normal-weight counterparts.[3] This could explain the higher blood pressure levels found in OA.

A study in adults reported a FMD of 9.4% ± 4.7%.[32] A meta-analysis by Dias et al.[3] identified a FMD of 6.0% ± 0.69% in adolescents with obesity, compared to 12.32% ± 3.14% in NWA.[3] This data corroborates our findings, showing an impaired vascular reactivity in OA compared with NWA (6.17 ± 2.72% and 9.37 ± 2.20%, respectively).

FMD is an indirect measure of NO bioavailability,[26,28,32] since it simulates an ischemic environment, and later, vasodilation. Vessel occlusion leads to the release of adenosine, endothelium-derived hyperpolarizing factor, hydrogen ions, among other substances, with the aim of restoring blood perfusion through microcirculation dilation. In this method, when the cuff is deflated, circulation is restored with increased blood supply to the ischemic region,

causing "reactive hyperemia". The shear stress caused by the increase in blood flow and its velocity leads to the release of vasodilatory substances by the endothelium, such as NO, via activation of the endothelial NO synthase (eNOS) enzyme, leading to vascular smooth muscle relaxation and consequent increase in arterial diameter. A lower relaxation capacity leads to endothelial dysfunction.[26,28,32] A lower vasodilation may occur in boys than in girls and there is variation of endothelial function during the menstrual cycle.[28] Thus, we performed the tests in the first stage of the menstrual period. EndoPAT ® was evaluated by Radke et al. in relation to pubertal staging.[33] A lower RHI was observed in the prepuberty in comparison with those at Tanner IV-V puberty stages, with an index ranging from 1.11 to 1.70. The cut off for adults is 1.35, which could be used to identify those individuals with endothelial dysfunction in the microcirculation. This technique was developed to be examiner-independent. It is known that, due to location of the cuff to be inflated, the vasodilation of microcirculation obtained is not totally dependent on NO. Therefore, while EndoPAT® measures the endothelial function of the microcirculation, the FMD evaluates the endothelial function of the conductance arteries. It is possible that the results are comparatively discrepant, but complementary, since these methods evaluate different systems.[28] In the adolescents evaluated in this study, there was no difference in this measure between OA and NWA, so we could not identify complementarity between EndoPAT® and FMD.

Another relevant factor in the study was the correlation between WC and vascular reactivity. An increased WC is a risk predictor for CVD,[15,34] and this is named as "visceral adiposity syndrome".[4,34] With the increase of the visceral adiposity, there is an increase in pathogenic fat depots and worsening of the vascular reactivity. Visceral fat distribution is a predictive factor for hypertension, greater than the generalized fat increase itself. Sympathetic nervous system seems to be related to different components of visceral adiposity syndrome, generating a real increase in sympathetic activity[34] and an increased risk of hypertension in these patients.

Although there was no difference in AHI between the two groups studied, there was a prevalence of 86.6% and 50% of OSA, and of 35% and 0% of MetS in OA and NWA, respectively. The greater presence of OSA and MetS may have contributed to the increase of SBP in this group, which may be modulated by increased sympathetic tonus. This has already been observed by Trombetta et al., who reported higher sympathetic activity and reduced baroreflex control in adult patients with MetS associated with OSA.[10]

In the current study, we observed that OA exhibited decreased VO_2peak suggesting increased cardiovascular risk. Indeed, there is strong evidence that obesity is associated with a worse prognosis in adolescents with reduced functional capacity and presence of cardiometabolic comorbidities. Preventive measures are necessary in these individuals with endothelial dysfunction, stimulating physical activity and a healthy diet aiming to reduce WC and BP.

Limitations

Our study has several limitations. First, considering that in girls there is variation of endothelial function during the menstrual cycle,[28] and although we performed the test in the first stage of the menstrual cycle, some girls had just had menarche and, therefore, did not have menstrual regularity or knowledge of their cycle. Second, since there is no consensus on the criteria for diagnosing OSA at the age from 13 to 18 years, in the present study, like others,[35,36] we assumed pediatric values. The criteria used up to 13 years were extended up to the age of 18, based on the AASM manual for Scoring of Sleep and Associated Events.[23]

Conclusion

In the sample studied, obesity was an important risk factor for development of MetS and lead to endothelial dysfunction, which is the onset of atheroma plaque. In addition, increased WC and SBP are predictors of endothelial dysfunction in adolescents. OSA was detected in most adolescents, regardless of obesity.

Acknowledgements

The authors wish to thank to all participants of the study. Special thanks to the staff from the Cardiopulmonary Rehabilitation Department of Universidade Nove de Julho (UNINOVE), especially Simone Dal Corso, PhD, for the logistical support and assistance with Cardiopulmonary Exercise Testing (CPET).

This work was supported by Universidade Nove de Julho (UNINOVE), São Paulo, Brazil. MFH was supported by Universidade Nove de Julho (UNINOVE), FXC was supported by FAPESP (#2015/ 03274-0 and #2016/16831-7) and Coordenação de Aconselhamento de Pessoal de Nível Superior (CAPES). RRPL-V, LV and KYK were supported by Coordenação de Aconselhamento de Pessoal de Nível Superior (CAPES). EFO and FMCC were supported by FAPESP (#15/11738-6 to EFO). ICT and LVFO were supported by Conselho Nacional de Pesquisa (CNPq #302809/2018-0 to ICT, CNPq #313053/2014-6 to LVFO, respectively). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Author Contributions

Conception and design of the research: Hussid MF, Cepeda FX, Consolim-Colombo FM, Trombetta IC; Data acquisition: Jordão CP, Lopes-Vicente RRP, Katayama KY, Oliveira EF, Oliveira LVF; Analysis and interpretation of the data: Hussid MF, Cepeda FX, Oliveira LVF, Trombetta IC; Statistical analysis, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Hussid MF, Cepeda FX, Trombetta IC.

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 article is part of the thesis of master submitted by Maria Fernanda Hussid, from Universidade Nove de Julho - UNINOVE.

References

1. World Health Organization. (WHO). Ending Childhood Obesity. Geneva;2016.
2. Brasil. Ministério da Saúde, Instituto Brasileiro de Geografa e Estatística. (IBGE). Pesquisa Nacional de Saúde do Escolar 2015. Brasília-DF:IBGE; 2016. 132 p.
3. Dias KA, Green DJ, Ingul CB, Pavey TG, Coombes J.S. Exercise and Vascular Function in Child Obesity: A Meta-Analysis. Pediatrics. 2015,136(3), e648–e659.
4. Mongraw-Chaffin, M, Foster MC, Kalyani RR, Vaidya D, Burke GL, Woodward M,et al. Obesity severity and duration are associated with incident metabolic syndrome: Evidence against metabolically healthy obesity from the multi-ethnic study of atherosclerosis. J. Clin. Endocrinol. Metab. 2016, 101(11), 4117–24.
5. Cristina D, Masquio L, Ganen ADP, Munhoz R, Sanches PDL, Corgosinho FC,et al. Cut-off values of waist circumference to predict metabolic syndrome in obese adolescents. Nutr Hosp. 2015; 31(4):1540-50.
6. Vanhoutte PM. Endothelial dysfunction: a multifaceted disorder. Am J Physiol Hear Circ Physiol. 2006;291(3):H985-H1002.
7. Thijssen DH, Black MA, Pyke KE, Padilla J, Atkinson G, Harris RA, et al. Assessment of flow-mediated dilation in humans: a methodological and physiological guideline. Am J Physiol Heart Circ Physiol. 2011;300(1); H2-12.
8. Gileles-Hillel A, Alonso-Alvarez ML, Kheirandish-Gozal L, Peris E, Cordero-Guevara JA,et al. Inflammatory markers and obstructive sleep apnea in obese children: the NANOS study. Mediat Inflamm. 2014; 2014:1-9.605280
9. Bhushan B, Ayub B, Loghmanee DA, Billings KR. Metabolic alterations in adolescentes with obstructive sleep apnea. Int J Pediatr Otorhinolaryngol. 2015;79(12):2368-73.
10. Trombetta IC, Somers VK, Maki-Nunes C, Drager LF. Syndrome — Implications for Cardiovascular Risk. Sleep.2010;33(9):1193-9.
11. Bhattacharjee R, Kim J, Alotaibi WH, Kheirandish-Gozal L, Capdevila OS, Gozal D. Endothelial dysfunction in children without hypertension: Potential contributions of obesity and obstructive sleep apnea. Chest. 2012, 141(3):682-91.
12. Brasil.Ministério da Saúde. Orientações para o atendimento à saúde do adolescente. Brasília, DF; 2008.
13. Brasil. Ministério da Saúde. Orientações para o atendimento à saúde do adolescente. Brasília, DF; 2008.
4. World Health Organization. (WHO).The WHO Child Growth Standards. Geneva; 2023.
15. Consensus Statements – IDF Consensus definition of the metabolic in children. (Acessed in 2019 Jun 12).Available from: idf.org/e-library/consensus-statement/61-idf-consensus-definition.html
16. Fernandez JR, Redden DT, Pietrobelli A, Allison DB. Waist circumference percentiles in nationally representative samples of african-american, european-american, and mexican-american children and adolescents. J Pediatr.2004; 145(4):439-44.
17. Coutinho CA, Longui CA, Monte O,CondeW, Kochi C. Measurement of neck circumference and its correlation with body composition in a sample of students in São Paulo, Brazil. Horm Res Paediatr. 2014, 82(3):179-86.
18. Brasil.Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Atenção Básica. Hipertensão arterial sistêmica para o Sistema Único de Saúde. Brasília (DF); 2006. (citado em 2019 20 jan). Available from: http://dab.saude.gov.br/docs/publicacoes/cadernos_ab/abcad15.pdf
19. Urbina E, Alpert, B, Flynn J, Hayman L, Harshfield GA, Jacobson M, et al. Ambulatory Blood Pressure Monitoring in Children and Adolescents : Recommendations for Standard Assessment A Scientific Statement From the American Heart Association Atherosclerosis , Hypertension , and Obesity in Committee of the Council on Cardiovascular Disease in the Young and the Council for High. Hypertension. 2008;52(3):433-51.
20. Nobre F, Saad CI R ,Giorgi DM, Mion D ,Sociedade Brasileira de Cardiologia, Sociedade Brassileira de Hipertensão, Sociedade Brasileira de Nefrologia. VI Diretrizes Brasileiras. Arq Bras Cardiol. 2010;95:1-51,
21. The Report of an American Academy of Sleep Medicine Task Force. Sleep related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep. 1999;22(5):667-89.
22. Iber C, Ancoli-Israel S, Chesson A, Quan SF. The AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications.American Academy of Sleep Medicine;2007.
23. Berry, R.B.; Budhiraja, R.; Gottlieb, D.J.; Gozal, D.; Iber, C.; Kapur, V.K.; Marcus, C.L.; 23.Mehra, R.; Parthasarathy, S.; Quan, S.F.; et al. Rules for Scoring Respiratory Events in Sleep : Update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. J Clin Sleep Med. 2012;8(5):597-619.
24. Neder JA, Nery LE. Teste de exercício cardiopulmonar. J Pneumol .2002, 28(Supl 3):166-206.
25. Neder JA, Nery LE, Castelo A, Andreoni S, Lerario MC, Sachs A et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomised study. Eur Respir J. 1999;14(6):1304-13.
26. Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller O, Sullivan ID et al. Noninvasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet. 1992;340(8828):111-5.
27. Bonetti PO, Pumper GM, Higano ST, Holmes DR, Kuvin JT, Lerman A. Noninvasive identification of patients with early coronary atherosclerosis by assessment of digital reactive hyperemia. J. Am. Coll. Cardiol. 2004;44(11):2137-41.
28. Bruyndonckx L, Hoymans VY, Van Craenenbroeck AH, Vissers DK, Vrints CJ, Ramet J, et al. Assessment of Endothelial Dysfunction in Childhood Obesity and Clinical Use. Oxid Med Cell Longev. 2013, 2013: 1–19. 174872.
29. Redline S, Tishler P V, Schluchter M, Aylor J, Clark K, Graham G. Risk Factors for Sleep-disordered Breathing in Children Associations with Obesity , Race , and Respiratory Problems African Americans appears to be independent of the effects of obesity or respiratory problems . Red-. Am J Respir Crit Care Med. 1999;159(5Pt1): 1527–32.
30. Hopkins ND, Dengel DR, Green DJ, Age and sex relationship with flow-mediated dilation in healthy children and adolescents. J. Appl. Physiol. 2015;119(8):926-33.
31. Wilk G, Osmenda G, Matusik P, Nowakowski D, Jasiewicz-Honkisz B, Ignacak A, et al.Endothelial function assessment in atherosclerosis: Comparison of brachial artery flow-mediated vasodilation and peripheral arterial tonometry. Pol Arch Med Wewn. 2013;123(9):443-52.
32. Consolim-Colombo, F.M.; Costa-Hong V., Katayama K.Y. Método de investigação da função endotelial em humanos. In: Endotélio e Doenças Cardiovasculares,São Paulo:Atheneu; 2016.
33. Radtke T, Khattab K, Eser P, Kriemler S, Saner H, Wilhelm M. Puberty and microvascular function in healthy children and adolescents. J Pediatr. 2012; 161(5):887-91.
34. Lopes HF, Correa Gianella ML, Consolim Colombo FM, Egan BM,Visceral adiposity syndrome .Diabetol Metab Syndr. 2016 Jul 1;8:40.
35. Oliveira, V.X.N.; Teng, A.Y. The Clinical Usefulness of Sleep Studies in Children. Paediatr. Respir Rev. 2016;17:53-6.
36. Marcus CL, Brooks LJ, Ward SD, Draper KA, Gozal D, Halbower AC, et al. The clinical usefulness of sleep studies in children.Diagnosis and Management of Childhood Obstructive Sleep Apnea Syndrome. Pediatrics. 2012;130(3):e714-e755.

Cardiovascular Disease Prevention in Adolescence: New Possibilities

Mariana Xavier e Silva

Faculdades Pequeno Príncipe, Curitiba, PR – Brazil

Short Editorial related to the article: Visceral Obesity and High Systolic Blood Pressure as the Substrate of Endothelial Dysfunction in Obese Adolescents

It is currently known that the atherosclerosis process starts in childhood.[1] Thus, in order to decrease the number of cardiovascular events in the adult population, it was necessary to establish strategies aimed at preventing the development of risk factors in children.[2] Of these, obesity is one of the most accountable elements. Obesity and its consequences, especially in adolescents, has been an increasingly frequent reality in cardiologists' offices.[3] Studies have shown that a high body mass index means a greater probability of developing chronic diseases, including, and among them, atherosclerosis, systemic arterial hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome and comorbidities, such as obstructive sleep apnea.[4,5] These risk factors, also during growth and development, tend to join and act in favor of cardiovascular disease.[6]

Overweight and obesity in children and adolescents are indeed a matter of concern. A close look shows that, in the last twenty years, their proportion has greatly increased in several countries.[3,7,8] Adolescence is characterized by significant changes in body composition, especially during puberty. The follow-up and monitoring are essential since weight, body fat and lean mass are predictive characteristics of the development of cardiovascular risk factors in adult life.[2,4] This age group, within this scenario, has a five-fold greater risk of excessive adiposity in the future, thus becoming a marker of increased cardiometabolic risk.[9]

Obesity can also aggravate other risk factors. In adolescents, it is associated with higher blood pressure, especially systolic blood pressure.[10] In Brazil, the results of the ERICA study showed that almost 1/5 of the prevalence of hypertension in adolescents in Brazil can be attributed to obesity. According to this study, in absolute numbers, about 200,000 Brazilian adolescents would not have high blood pressure if they were not obese.[7] In children, blood pressure levels, in addition to being associated with overweight, also correlate with body fat distribution. There is a direct association between waist circumference measures and blood pressure values.[1]

Likewise, the childhood obesity epidemic is also responsible for the occurrence of diseases that impact metabolism.[3] Temporary alterations in metabolic risk factors occur in childhood and adolescence, years before the onset of cardiovascular disease clinical events.[11] The aggregation of multiple risk factors, such as central obesity, dyslipidemia, hypertension and insulin resistance, among others, constitute the metabolic syndrome.[12] This syndrome, in Pediatrics, remains a controversial matter regarding its criteria.[6] Therefore, it is essential to contextualize that puberty is a sensitive window of time for the development of the pathophysiological origins of the metabolic syndrome, since it incorporates several hormonal and body alterations. These include the accumulation of fat and reduced insulin sensitivity, which contribute to the outcome of the established inflammatory status.[11]

Understanding obesity in this population, included in the generated inflammation environment, shows the process of atherosclerosis has its start, acceleration and progression.[11] Endothelial dysfunction is an early pathophysiological indicator of this disease and, therefore, shows the doctor treating the adolescent that it is necessary to intervene, aiming to minimize the possibility of increased morbidity and mortality related to cardiovascular system events.[11] Pathological and physiological alterations in the vascular endothelium may be found in obese children even if they have not yet developed metabolic syndrome. For this reason, the protection of vascular endothelial function is crucial and has become a target for the treatment of this disease.[13]

Among the modifiable environmental factors that can interfere with risk, the consumption of the obesogenic diet is considered one of the main factors.[3] However, other potentially plausible factors, such as short sleep duration, have been gaining more and more attention in recent years.[5] Obstructive sleep apnea syndrome is closely related to excessive weight gain, metabolic and cardiovascular disorders.[11] Patients with obstructive apnea have recurrent hypoxic episodes during sleep, which lead to oxidative stress in the blood vessels and thus, increase inflammation. Many researchers seek to investigate whether the negative potential of inflammatory mediators could lead to vascular injury, with endothelial dysfunction then being mediated by this process.[14,15]

In this issue of the Brazilian Archives of Cardiology, the authors[11] investigate the association between obese adolescents, metabolic syndrome, endothelial dysfunction and obstructive sleep apnea. Also, there was an interest in exploring the association between the last two, since endothelial alteration is an early marker of cardiovascular risk. The group comprised by obese adolescents, when compared to the group comprised by adolescents with normal weight, showed a higher abdominal circumference index, body fat, blood pressure, triglycerides and LDLc.

Keywords

Cardiovascular Diseases/prevention and control; Cardiovascular Diseases/trends; Adolescent; Atherosclerosis; Risk Factors; Childhood.

Mailing Address: Mariana Xavier e Silva •
Rua das Corruiras, 80 s 26. Postal Code 81020-570, Novo Mundo, Curitiba, PR - Brazil
E-mail: marianaxaviermx@gmail.com

DOI: https://doi.org/10.36660/abc.20200556

Hence, they found lower HDLc levels and functional capacity. It was demonstrated that 35% of the adolescents met the criteria for metabolic syndrome. Another interesting finding was the association between endothelial dysfunction and higher values for both abdominal circumference and systolic blood pressure. In this study, the presence of obstructive sleep apnea was not different between the two assessed groups. Consequently, the study ends by assuming that obesity in adolescents increased the risk for metabolic syndrome and endothelial dysfunction. Higher values of abdominal circumference and systolic blood pressure levels support this finding. However, regardless of the obesity factor, apnea was observed in both groups.

Thus, in view of the presented facts, it can be concluded that every effort is important in the prevention of cardiovascular diseases in adults. That begins in childhood, with the identification of risk factors and early approach. The intention is to prevent endothelial dysfunction, which is an atherosclerosis substrate. Obesity can precede future metabolic disorders and is closely associated with the development of chronic diseases and comorbidities.

References

1. Genovesi S, Giussani M, Orlando A, Battaglino MG, Nava E, Parati G. Prevention of cardiovascular diseases in children and adolescents. High Blood Press Cardiovasc Prev. 2019; 26(3):191-7.
2. Araújo AJS, Santos ACO, Prado WL. Body composition of obese adolescents: association between adiposity indicators and cardiometabolic risk factors. J Hum Nutr Diet. 2017; 30(2):193-202.
3. Bussler S, Penke M, Flemming G, Elhassan YS, Kratzsch J, Sergeyev E, et al. Novel Insights in the Metabolic Syndrome in Childhood and Adolescence. Horm Res Paediatr. 2017; 88(3-4):181-93.
4. Afshin A, Forouzanfar MH, Reitsma MB, Sur P, Estep K, Lee A, et al. Health effects of overweight and obesity in 195 countries over 25 years. N Engl J Med. 2017; 377(1):13-27.
5. Fu J, Wang Y, Li G, Han L, Li Y, Li L, et al. Childhood sleep duration modifies the polygenic risk for obesity in youth through leptin pathway: the Beijing Child and Adolescent Metabolic Syndrome cohort study. Int J Obes. 2019; 43(8):1556-67.
6. Ahrens W, Moreno L, Mårild S, Molnár D, Siani A, Henauw S, et al. Metabolic syndrome in young children: Definitions and results of the IDEFICS study. Int J Obes. 2014; 38:S4-14.
7. Bloch KV, Klein CH, Szklo M et al. ERICA: Prevalences of hypertension and obesity in Brazilian adolescents. Rev Saude Publica. 2016; 50(supl 1):1s-12s.
8. Aslan E, Sert A, Buyukinan M, Pirgon MO, Kurku H, Yilmaz H, et al. Left and right ventricular function by echocardiography, tissue Doppler imaging, carotid intima-media thickness, and asymmetric dimethyl arginine levels in obese adolescents with metabolic syndrome. Cardiol Young. 2019; 29(3):310-8.
9. Chung ST, Onuzuruike AU, Magge SN. Cardiometabolic risk in obese children. Ann N Y Acad Sci. 2018; 1411(1):166-83.
10. Guzman-limon M. Pediatric hypertension blood pressure hypertension pediatrics guidelines. Pediatr Clin North Am. 2019;66(1):45-57.
11. Hussid MF, Cepeda FX, Jordão CP, Lopes-Vicente RRP, Virmondes L, Katayama KY, et al. Obesidade Visceral e Hipertensão Sistólica como Substratos da Disfunção Endotelial em Adolescentes Obesos. Arq Bras Cardiol. 2021; 116(4):795-803.
12. Börnhorst C, Russo P, Veidebaum T, Tornaritis M, Molnar D, Lissner L, et al. Metabolic status in children and its transitions during childhood and adolescence - The IDEFICS/I.Family study. Int J Epidemiol. 2019; 48(5):1673-83.
13 Wei Y, Liu GL, Yang JY, Zheng RX, Jiang LH, Li YP, et al. Association between metabolic syndrome and vascular endothelium dysfunction in children and adolescents. Genet Mol Res. 2014; 13(4):8671-8.
14. Blechner M, Williamson AA. Consequences of obstructive sleep apnea in children. Curr Probl Pediatr Adolesc Health Care. 2016; 46(1):19-26.
15. Jia L, Fan J, Cui W, Liu SA, Li NA, Lau WB, et al. Endothelial cell-derived microparticles from patients with obstructive sleep apnea hypoxia syndrome and coronary artery disease increase aortic endothelial cell dysfunction. Cell Physiol Biochem. 2017; 43(6):2562-70.

Increased Pulmonary Arterial Stiffness and Impaired Right Ventricle-Pulmonary Artery Coupling In PCOS

Ozge Ozcan Abacioglu,[1] Erdinc Gulumsek,[2] Hilmi Sumbul,[2] Mehmet Kaplan,[1] Fethi Yavuz[1]

Health Sciences University, Adana Research and Training Hospital, Department of Cardiology,[1] Adana - Turkey

Health Sciences University, Adana Research and Training Hospital, Department of Internal Medicine,[2] Adana - Turkey

Abstract

Background: **Polycystic ovary syndrome (PCOS) is the most common endocrine-metabolic disease in women in reproductive age, and occurs in one of 10 women. The disease includes menstrual irregularity and excess of male hormones and is the most common cause of female infertility. Dyspnea is a frequent symptom and is often thought to be due to obesity, and whether it is due to cardiac dysfunction is unknown.**

Objective: **To evaluate right ventricle-pulmonary artery (RV-PA) coupling and pulmonary arterial stiffness in patients with PCOS.**

Methods: **44 PCOS patients and 60 controls were included; venous blood samples were taken for laboratory tests and 2-D, m-mode and tissue doppler transthoracic echocardiography were performed for all the participants. P<0,05 was considered as statistically significant.**

Results: **When compared to the control group, PCOS patients had higher pulmonary artery stiffness values (p=0,001), which were positively correlated with HOMA-IR (r=0,545 and p<0,001). RV-PA coupling was also impaired in 34% of the study patients.**

Conclusion: **Pulmonary artery stiffness is increased and RV-PA coupling is impaired in patients with PCOS. (Arq Bras Cardiol. 2021; 116(4):806-811)**

Keywords: **Diseases of the Endocrine System; Arterial Stiffness; Female infertility; Obesity; Dyspnea; Pulmonary hypertension.**

Introduction

Polycystic ovary syndrome (PCOS) is considered a multisystemic, reproductive and metabolic disease. It is the most common endocrinological disorder in women of reproductive age and its prevalence varies between 6-15% according to different diagnostic criteria. In order to clarify the diagnostic criteria of PCOS, three major consensuses have been established to date (National Institute of Health- NIH, Rotterdam and Androgen Excess Society). The presence of polycystic ovaries, menstrual irregularity, hirsutism, obesity and insulin resistance (IR) contribute to the clinical presentation of PCOS.[1] Women with PCOS have an adverse cardiovascular risk profile including dyslipidemia, hypertension and also endothelial dysfunction and coronary artery calcification.[2,3] Recent studies have shown that asymptomatic impairment of left ventricular (LV) function in young women is associated with obesity and IR rather than the sex hormone disturbances associated with PCO and in another study, LV mass was found to be higher in PCOS patients.[2-4]

Pulmonary artery stiffness (PAS) has been developed as a relatively new Doppler echocardiographic parameter to evaluate the pulmonary artery vasculature and mechanics.[5,6] Its association with right ventricular (RV) function and ability to predict functional capacity in pulmonary hypertension has been demonstrated. PAS is increased early in pulmonary hypertension development, so studies suggest that this biomarker may be used for early disease detection.

The right ventricle - pulmonary artery coupling is an indicator of pulmonary arterial compliance and its impairment is a result of reduced pulmonary artery compliance.[7] Studies suggested that decreased compliance plays a critical role in the pathogenesis of pulmonary artery hypertension (PAH) so that RV-PA coupling is clinically important, because of its association with increased mortality in patients with PAH.

The aim of this study was to investigate pulmonary artery stiffness and RV-PA coupling in patients with PCOS.

Methods

Study population

The study cohort consisted of 104 patients recruited from the Internal Diseases policlinic of Adana City Education and

Mailing Address: Ozge Ozcan Abacioglu •
Adana City Education and Research Hospital - Adana City Hospital Adana 01001 - Turkey
E-mail: ozgeozcan83@yahoo.com.tr
Manuscript received November 04, 2019, revised manuscript February 12, 2020, accepted April 08, 2020

DOI: https://doi.org/10.36660/abc.20190762

Research Hospital between March 2019 and September 2019. Data on demographic characteristics, medical history and medication use were obtained and patients with coronary artery disease, hypertension, diabetes mellitus, valvular heart disease rather than mild diastolic dysfunction, diagnosis or clinical findings (snoring, excessive daytime sleepiness or witnessed apnea) of obstructive sleep apnea syndrome, pulmonary artery hypertension, respiratory disease, right ventricular systolic dysfunction and poor echocardiographic imaging were excluded. Body mass index was calculated as the weight in kilograms divided by the squared height in meters. NIH criteria: clinical and/or biochemical hyperandrogenism, ovarian dysfunction (oligo-anovulation and /or polycystic ovaries) and exclusion of other causes such as Cushing syndrome, tumors etc., were used for diagnosis. The study population was asymptomatic and 77% presented with hirsutism, 32% with menstrual irregularity, 6% with acne, 6% with infertility and 6% with obesity. HFpEF (heart failure with preserved ejection fraction) score was 0 or 1 in 91% of the participants and the possibility of heart failure was low in the groups. 13 (29%) of PCOS patients were undergoing different treatments. Only one of them was using metformin. Mean disease duration was 31 months. The control group consisted of patients admitted to the polyclinic with similar symptoms but who did not meet the criteria for PCOS, of which 66% with menstrual irregularity, 20% with acne and 14% with infertility. These were due to diet, hormonal disorder and stress; fat restriction in the diet, anxiety treatment and prolactin lowering medications were administered and symptoms were relieved. The Adana City Education and Research Hospital approved the study protocol and this study was performed in accordance with the Declaration of Helsinki principles.

Echocardiography

A complete transthoracic echocardiographic evaluation was performed using commercially available ultrasonographic equipment according to recommendations of the American Society of Echocardiography.[8] TTE examinations included M-mode, two dimensional, Doppler flow assessments and pulsed-wave tissue Doppler imaging measurements. LV ejection fraction (LVEF), posterior wall (PW) and interventricular septal thickness (IVS) were determined. Tricuspid early and late diastolic velocities, systolic pulmonary arterial pressure, maximal pulmonary velocity were determined. Tricuspid annular plane systolic excursion (TAPSE), a measure of RV performance, was measured using m-mode analysis in the RV-focused apical four chamber view. Pulmonary artery acceleration time (PAAT), was acquired from the parasternal long axis view of the RV outflow at the level of the pulmonary valve using a published protocol for PAAT image acquisition.

Pulmonary artery stiffness was assessed in the parasternal short axis view using pulsed-wave Doppler and calculated according to the following formula: the ratio of maximum flow velocity shift of pulmonary flow to pulmonary acceleration time.[9]

The relationship between RV contractility and RV afterload is often referred to as RV-PA coupling. Contractility refers to load independent or intrinsic cardiac function, while afterload refers to the opposition to ventricular ejection. RV- PA coupling was calculated according to the following formula: TAPSE / SPAP and when a ratio <1.6 was obtained, it was characterized as impaired coupling.[10]

The echocardiographic measurements were performed by two blinded echocardiographers. The averages of measurements were calculated.

Laboratory analysis

Laboratory analysis included routine complete blood count, biochemistry and insulin levels for both the study and control groups. Serum lipid levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides (TG) were measured using xylidine blue with an endpoint colorimetric method. The Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated using fasting blood glucose level with fasting insulin level with at least 8-10 hours of fasting and according to following formula: fasting glucose level (mg /dL) x fasting insulin level (uIU/mL) /405. A HOMA score ≥2.5 was considered as positive insulin resistance.

Statistical analysis

All statistical analyses were performed using SPSS 17 (SPSS, Inc., Chicago, Illinois, USA). The study variables were analyzed using analytical methods (Kolmogorov-Smirnov test) to determine normal distribution and were expressed as mean ± standard deviation (mean ± SD) or numbers and percentages. The Mann-Whitney U test was used for the comparison of 2 groups with a non-normal distribution of variables and the chi-square test was used for the comparison of qualitative data. Comparisons of the continuous variables between groups were performed using the independent samples t-test, as appropriate, and associations between variables were carried out using Pearson 's product moment test. A two-tailed p value of less than 0.05 was considered as significant. Interobserver reproducibility was measured with Kendall's tau b correlation coefficient.

Results

The PCOS group's mean age was 22 ± 5 years, while the control group was 24 ± 5 years. Age and body mass index were statistically similar in the groups (p=0.329 and 0.210 respectively). The baseline demographic characteristics and laboratory parameters of the study groups are shown in Table 1.

Left and right ventricular echocardiography characteristics are shown in Table 2. LV ejection fraction, interventricular septum and posterior wall thickness, tricuspid early (E) and late (A) diastolic velocities, systolic pulmonary artery pressure (SPAP) and maximum pulmonary artery velocities were similar between groups. TAPSE was lower

Table 1 – Baseline demographic features and laboratory parameters of groups, and statistical analysis

	PCOS group n=44 (mean ± SD)	Control group n=60 (mean ± SD)	p-value
Age, years	22 ± 5	24 ± 5	0.210
BMI, kg/ m²	24.86 ± 2.74	24.26 ± 2.25	0.329
Glucose (mg/ dL)	96.45 ± 12.52	90.16 ± 1.48	0.279
Urea (mg / dL)	20.22 ± 5.53	23.38 ± 3.96	0.233
Sodium (mmol / L)	139.25 ± 1.72	137.60 ± 0.52	0.114
Potassium (mmol /L)	4.43 ± 0.29	4.33 ± 0.14	0.568
Calcium (mg / dL)	9.75 ± 0.35	9.62 ± 0.60	0.473
AST (u /L)	20.72 ± 5.06	19.88 ± 5.45	0.735
ALT (u /L)	16.90 ± 9.10	13.02 ± 2.01	0.354
LDL (mg /dL)	119.25 ± 22.81	111.16 ± 32.26	0.580
HDL (mg dL)	46.13 ± 13.28	42.30 ± 15.46	0.317
Triglycerides (mg /dL)	106.30 ± 78.40	91.66 ± 50.63	0.757
WBC (10^3 /µL)	7.60 ± 1.76	8.44 ± 2.79	0.318
HGB (g /dL)	12.90 ± 0.81	11.85 ± 2.10	0.238
PLT (10^3 /µL)	277.90 ± 69.23	272.85 ± 33.25	0.853
HOMA-IR	3.12 ± 2.00	2.16 ± .52	0.023

BMI: body mass index; AST: aspartate transaminase, ALT: alanine transaminase, LDL: low-density lipoprotein, HDL: high-density lipoprotein, WBC: white blood count, HGB: hemoglobin, PLT: platelets, HOMA-IR: homeostatic model for insulin resistance.

and pulmonary acceleration time was shortened in the study group and the difference was statistically significant ($p<0.001$ and $p= 0.001$, respectively).

Pulmonary artery stiffness (PAS) levels were higher in the PCOS group and PAS had a significantly positive correlation with HOMA-IR ($r=0.545$ and $p<0.001$) (Table 2 and Figure 1). Six patients (46%) with insulin resistance had higher PAS values than controls. The subgroup analysis of study patients who received treatment and those who received no treatment showed that pulmonary artery stiffness was higher in the non-treatment group (PAS= 5.15 ± 0.99 and 5.75 ± 1.02 respectively) but the difference was not statistically significant ($p=0.084$).

RV-PA coupling was impaired in 15 (34%) of the study group with mean levels 1.09 ± 0.23 and p value was significant between the two groups ($p<0.001$). Thirteen of these 15 patients were not receiving any treatment and the difference in terms of RV-PA coupling values between the subgroups, treated or nontreated, was also statistically significant. RV-PA coupling (mean ± SD) = 1.20 ± 0.22 for the treated group and 1.05 ± 0.22 for nontreated group. The p value was 0,048.

Kendall's tau b was 0.961 for PAS and 0.790 for RV-PA coupling.

Discussion

It is well known that the risk of cardiovascular diseases is elevated in patients with PCOS due to increased insulin resistance and impaired glucose tolerance. Previously reported findings about insulin metabolism and resistance provide new clues in the treatment of PCOS and related complications.[11]

The clinical manifestations of insulin resistance are; HT, dyslipidemia and type 2 DM. Asymptomatic effects are endothelial dysfunction, procoagulant status, proinflammatory condition and smooth muscle cell proliferation. Ergun et al. found that patients with metabolic syndrome had higher aortic stiffness values than controls. The mechanism that shows how insulin resistance increases stiffness may be explained by its asymptomatic effects.[12]

Wang et al.[4] reported in the CARDIA women's study that polycystic ovary syndrome is associated with higher left ventricular mass index and in another study, distinct abnormalities in both cardiovascular and metabolic features in PCOS were observed at an early age.[13,14] These differences are reflected by an increased pulse pressure and a higher left ventricular end-diastolic but a lower tissue Doppler imaging of the right wall in systole. The results could indicate that women with PCOS already have subtle arterial dysfunction, which could lead to atherosclerosis in later life.

Pulmonary arterial stiffness and abnormal flow hemodynamics in pulmonary arterial hypertension are strongly associated with elevated right ventricular afterload and associated with disease severity and poor clinical outcomes in adults with PAH.[15-17] RV-PA coupling can describe RV compensation in pulmonary hypertension and also in left-sided cardiac conditions and its importance has risen alongside increasing recognition of the pivotal role that RV plays in many cardiopulmonary conditions.[18-20]

Table 2 – Left and right ventricular echocardiography characteristics of the study and control groups, and statistical analysis

	PCOS group n=44 (mean ± SD)	Control group n=60 (mean ± SD)	p-value
LVEF (%)	61.45 ± 5.76	61.00 ± 5.32	0.810
IVS (mm)	8.85 ± 1.07	8.98 ± 1.24	0.633
PW (mm)	8.34 ± 1.06	8.63 ± 1.47	0.329
E/E'	10.33 ± 1.57	10.39 ± 1.76	0.896
Tricuspid E velocity (cm/s)	80.25 ± 12.73	75.81 ± 12.20	0.140
Tricuspid A velocity (cm/s)	56.05 ± 8.33	56.25 ± 9.76	0.924
SPAP (mmHg)	19.04 ± 2.54	18.04 ± 1.74	0.064
AT (ms)	159.35 ± 24.08	179.17 ± 22.36	0.001
Maximum Pulmonary Velocity	87.38 ± 12.49	84.79 ± 6.21	0.299
TAPSE (cm)	2.18 ± 0.30	2.58 ± 0.25	<0.001
PAS	5.58 ± 1.05	4.80 ± 0.78	0.001
RV-PA coupling	1.09 ± 0.23	1.63 ± 0.31	<0.001

PCOS: polycystic ovary syndrome; LVEF: left ventricular ejection fraction; IVS: interventricular septal thickness; PW: posterior wall; SPAP: systolic pulmonary artery pressure; AT: Acceleration time; TAPSE: tricuspid annular plane systolic excursion; PAS: pulmonary artery stiffness; RV-PA: right ventricle-pulmonary artery.

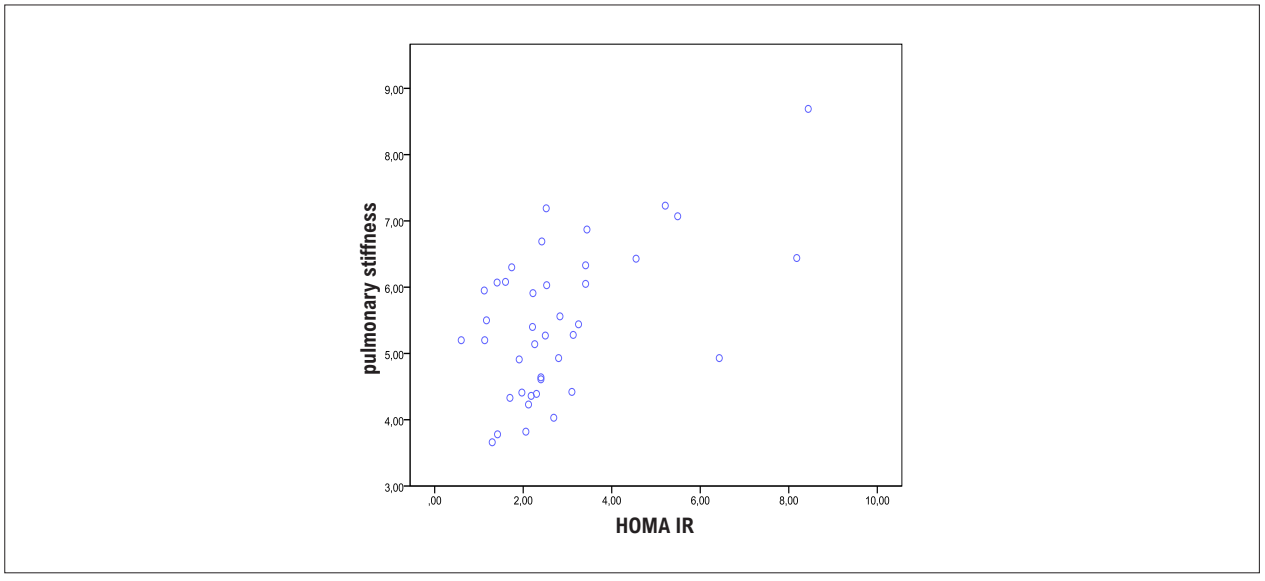


Figure 1 – *Correlation between HOMA-IR and PAS.*

We found that pulmonary artery stiffness, an indicator of pulmonary artery vasculature, was increased in PCOS and also associated with higher levels of HOMA-IR. RV-PA coupling, an indicator of pulmonary arterial compliance that has an important role in the pathogenesis of pulmonary arterial hypertension, is impaired in this patient group. This study is the first to evaluate pulmonary artery stiffness and RV-PA coupling in PCOS patients.

Considering all these complications and events, it has been shown in many previous studies and meta-analyses that the underlying pathology is insulin resistance. Although studies on the left ventricular and coronary artery disease are in the majority, pulmonary hypertension and right ventricular dysfunction have a significant place in mortality and establishes severe limitations for the patients' quality of life. PCOS patients should be informed about cardiac risk and routine cardiac examinations should be recommended.

Limitations

Our study had a few limitations. First, it was a single-center study with few participants. Another limitation of the current study was the short follow-up period. In addition, the evaluation of insulin resistance was only based on HOMA-IR. Further investigations with a longer duration and with larger groups are needed to assess the sustainability of the outcomes.

Conclusion

In summary, this study is the first to provide preliminary data that PCOS patients have increased pulmonary artery stiffness and impaired RV-PA coupling.

Author contributions

Conception and design of the research, Analysis and interpretation of the data, Statistical analysis, Obtaining financing, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Abacioglu OO; Acquisition of data: Abacioglu OO, Gulumsek E, Sumbul H, Kaplan M, Yavuz F.

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.

References

1. Ding T, Hardiman PJ., Petersen I, Wang FF , Qu F, and Baio G. The prevalence of polycystic ovary syndrome in reproductiveaged women of different ethnicity: a systematic review and meta-analysis. *Oncotarget.2017;8(56):96351-8.*
2. Baldani DP, Skrgatic L, Ougouage R.Polycystic Ovary Syndrome: Important Underrecognised Cardiometabolic Risk Factor in Reproductive-Age Women. *Int J Endocrinol.2015*. doi.org/10.1155/2015/786362
3. Barats SS, Benedictov II, Shadrin SA. Cardiovascular disorders, autonomic disorders and atherogenic dyslipoproteinemias in young women with the sclerotic ovary syndrome. *Kardiologiia*. 1984 Aug;24(8):34-7.
4. Wang ET, Ku IA, Shah SJ. et al. Polycystic Ovary Syndrome Is Associated with Higher Left Ventricular Mass Index: The CARDIA Women's Study J Clin Endocrinol Metab. 2012 Dec; 97(12): 4656–62.
5. Gupta A, Sharifov OF, Lloyd SG, Tallaj JA, Aban I, Dell'italia LJ, et al. Novel Noninvasive Assessment of Pulmonary Arterial Stiffness Using Velocity Transfer Function. *J Am Heart Assoc.* 2018 Sep 18;7(18):e009459
6. Friesen RM, Schäfer M, Ivy DD, Abman SH, Stenmark K, Browne LP, et al. Proximal pulmonary vascular stiffness as a prognostic factor in children with pulmonary arterial hypertension. *Eur Heart J Cardiovasc Imaging.* 2019 Feb 1;20(2):209-17.
7. 'Aubert R, Venner C, Huttin O, Haine D, Filippetti L, Guillaumot A, et al. Three-Dimensional Echocardiography for the Assessment of Right Ventriculo-Arterial Coupling. J *Am Soc Echocardiogr.* 2018 Aug;31(8):905-15.
8. Cheitlin MD, Armstrong WF, Aurigemma GP, Belle GA, Bierman FZ, Jack L Davis JL, et al.. ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography: Summary Article A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). J Am Coll Cardiol..2003;45(5) *doi:* 10.1016/S0735-1097(03)01065-9
9. E, M, UC, M, B, D, et al. Relationship between Pulmonary Artery Stiffness and Functional Capacity in Patients with Heart Failure with Reduced Ejection Fraction . *Korean Circ J*. 2017 Nov; 47(6): 929–38.
10. Kubba S, Davila CD, Forfia PR. Methods for Evaluating Right Ventricular Function and Ventricular-Arterial Coupling. *Prog Cardiovasc Dis.* 2016 Jul-Aug;59(1):42-51.
11. Wilde MA, Eising JB, Gunning MN, Koster MPH, Evelein AMV, Dalmeijer GW, et al. Cardiovascular and Metabolic Health of 74 Children From Women Previously Diagnosed With Polycystic Ovary Syndromein Comparison With a Population-Based Reference Cohort. *Reprod Sci*. 2018 Oct;25(10):1492-500.
12. http://www.istanbulsaglik.gov.tr/w/tez/pdf/kardiyoloji/dr_dilek_ergun.pdf
13. Kosmala W, O'Moore-Sullivan TM, Plaksej R, Kuliczkowska-Plaksej J, Przewlocka-Kosmala M, et al. Subclinical impairment of left ventricular function in young obese women: contributions of polycystic ovary disease and insulin resistance. *J Clin Endocrinol Metab*. 2008 Oct;93(10):3748-54
14. Simakova MA, Ryzhkov AV, Kyzymly AV, Naimushin AV, Lukinov VL, Moiseeva OM. Perspectives of using pulmonary arterial stiffness indicators to evaluate the prognosis of patients with pulmonary arterial hypertension. *Ter Arkh*.2018 Feb 14;90(1):86-92
15. Hsu S. Coupling Right Ventricular-Pulmonary Arterial Research to the Pulmonary Hypertension Patient Bedside. *Circ Heart Fail*. 2019 Jan;12(1):e005715
16. Sun W, Chan SY. Pulmonary Arterial Stiffness: An Early and Pervasive Driver of Pulmonary Arterial Hypertension. *Front Med (Lausanne)*. 2018 Jul 18;5:204.
17. Wang Z, Chesler NC. Pulmonary vascular wall stiffness: An important contributor to the increased right ventricular afterload with pulmonary hypertension. *Pulm Circ*. 2011 Apr-Jun;1(2):212-23.
18. Guihaire J, Haddad F, Boulate D, Decante B, Denault AY, Wu J, et al. Non-invasive indices of right ventricular function are markers of ventricular-arterial coupling rather than ventricular contractility: insights from a porcine model of chronic pressure overload. *Eur Heart J Cardiovasc Imaging*. 2013 Dec;14(12):1140-9.
19. Prins KW, Weir EK, Archer SL, Markowitz J, Rose L, Pritzker M, et al. Pulmonary pulse wave transit time is associated with right ventricular-pulmonary artery coupling in pulmonary arterial hypertension. *Pulm Circ*. 2016 Dec;6(4):576-85.
20. Tello K, Dalmer A, Axmann J, Vanderpool R, Ghofrani HA, Naeije R, et al Reserve of Right Ventricular-Arterial Coupling in the Setting of Chronic Overload. *Circ Heart Fail*. 2019 Jan;12(1):e005512.

Pulmonary Hypertension in Polycystic Ovarian Syndrome

Yogesh N. V. Reddy[1]

Divisão de Doenças Cardiovasculares, Clínica Mayo,[1] *Rochester - USA*

Short Editorial related to the article: Increased Pulmonary Arterial Stiffness and Impaired Right Ventricle-Pulmonary Artery Coupling In PCOS

Polycystic Ovarian Syndrome (PCOS) is a complex endocrinological syndrome that presents in women with obesity, insulin resistance and sex hormone abnormalities. It is intriguing that in otherwise 'idiopathic' pulmonary hypertension, there also seems to be a high prevalence of the same features of obesity, insulin resistance, and sex hormone abnormalities.[1-3] However, despite this overlap and a theoretical risk of pulmonary hypertension in PCOS, little is known about the intersection of the two conditions. Given the young age of patients at the time of PCOS diagnosis, only subtle impairments in left heart function have been consistently described,[4,5] with overt cardiovascular disease often manifesting many decades later.[6,7] But, surprisingly, little is known about subclinical right heart remodeling or pulmonary hypertension in this condition.

On this background, Abacioglu et al.[8] provide novel information on cardiac structural remodeling in patients with PCOS, with careful attention to right heart structure and function. They included 44 patients with PCOS and 60 matched controls who underwent comprehensive echocardiography and insulin resistance assessment by the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR). In addition to left heart measures of diastolic function, the authors also performed pulse wave Doppler of the right ventricular outflow tract to estimate pulmonary arterial stiffness, and used the well validated TAPSE/RVSP ratio to quantify RV-PA coupling.

The study cohort of PCOS and controls were well-matched regarding baseline age and overall body mass index (BMI). The PCOS group was on average young (mean age 22) with a normal mean BMI (24.9 kg/m^2) and showed absence of other cardiovascular risk factors, but insulin resistance was worse in the PCOS group, consistent with their underlying pathophysiology. Overall, there were no differences in left-sided systolic or diastolic dysfunction by echocardiography. However, pulmonary artery stiffness, right-sided function and RV-PA coupling was worse in the PCOS group. Pulmonary artery stiffness correlated with insulin resistance and tended to be higher in patients who were not undergoing treatment for PCOS.

Keywords

Polycystic Ovary Syndrome; Pulmonary Hypertension; Obesity; Insulin Resistance; Echocardiography/methods; Body Mass Index; Ventricular Remodeling.

Mailing Address: Yogesh N. V. Reddy •
Mayo Clinic - 200 1st St SW Rochester 55901 – USA
E-mail: reddy.yogesh@mayo.edu

DOI: https://doi.org/10.36660/abc.20210106

Although the study sample is small, the groups were well-matched in overall demographics apart from insulin resistance, allowing assessment of subclinical impairments secondary to PCOS. However, the differences between the groups were small and the evaluation of the long-term progression of these changes in RV-PA coupling to determine clinical significance is needed. Sex hormone alterations have also been identified in patients with either PAH or PCOS, and how these influence the abnormal RV-PA coupling in this sample is unknown.

These issues aside, this study provides important information on the potential role of PCOS in pulmonary hypertension in women. It is remarkable that despite modern advances, a large proportion of PAH cases remain idiopathic with a disproportionate effect on women. Given the shifting demographics of PAH to a more obese phenotype in modern times,[9] the role that metabolic syndrome, insulin resistance and obesity may have in pulmonary hypertension is a question of great public health importance. Visceral adiposity in particular is more strongly linked with insulin resistance and can be markedly different for the same BMI and preferentially worsens central hemodynamics in women.[10]

Whether differences in visceral adiposity in PCOS may underlie some of the observed right heart changes requires future studies. Weight loss in overweight patients, even in those without heart failure, may improve pulmonary artery pressures and central hemodynamics,[11] and given the central role of obesity in many patients with PCOS, this may have important therapeutic implications for long-term cardiovascular health.

An important caveat to echocardiographic studies such as this, is the systemic underestimation of the burden of left heart disease and early heart failure with preserved ejection fraction that is increasingly recognized in young overweight individuals.[12-14] Traditional echocardiographic parameters are not sensitive for early left heart remodeling and heart failure with preserved ejection fraction,[14,15] and if the left heart filling pressures are higher than expected, this can contribute to abnormal pulmonary artery stiffness. The PCOS group in this study was also somewhat atypical in the fact that the average BMI was that of non-obese individuals. Therefore, the finding that left ventricular diastolic function was not impaired in this study may not be generalizable to other PCOS cohorts where subclinical left heart remodeling has been previously reported.[10] Obesity is independently associated with progressive right heart remodeling,[16] abnormal RV-PA coupling, along with elevated left heart filling pressures.[13,14] Therefore in PCOS, the associated metabolic syndrome, obesity (12) and particularly visceral adiposity[17] may have a chronic remodeling effect on the heart and predispose to heart failure with preserved ejection fraction and associated pulmonary hypertension in the future. Given the large number of young individuals affected by PCOS, the study by Abacioglu et al.[8] should be an urgent call for further investigation into the relationship between PCOS and the future risk of pulmonary hypertension.

References

1. Austin ED, Cogan JD, West JD, Hedges LK, Hamid R, Dawson EP, et al. Alterations in oestrogen metabolism: implications for higher penetrance of familial pulmonary arterial hypertension in females. Eur Respir J. 2009/04/10 ed. 2009 Nov;34(5):1093–9.

2. Hansmann G, Wagner RA, Schellong S, Perez VA de J, Urashima T, Wang L, et al. Pulmonary arterial hypertension is linked to insulin resistance and reversed by peroxisome proliferator-activated receptor-gamma activation. Circulation. 2007 Mar 13;115(10):1275–84.

3. Heresi GA, Malin SK, Barnes JW, Tian L, Kirwan JP, Dweik RA. Abnormal Glucose Metabolism and High-Energy Expenditure in Idiopathic Pulmonary Arterial Hypertension. Ann Am Thorac Soc. 2017 Feb;14(2):190–9.

4. Wang ET, Ku IA, Shah SJ, Daviglus ML, Schreiner PJ, Konety SH, et al. Polycystic ovary syndrome is associated with higher left ventricular mass index: the CARDIA women's study. J Clin Endocrinol Metab. 2012 Dec;97(12):4656–62.

5. Tíras MB, Yalcìn R, Noyan V, Maral I, Yildîrìm M, Dörtlemez O, et al. Alterations in cardiac flow parameters in patients with polycystic ovarian syndrome. Hum Reprod Oxf Engl. 1999 Aug;14(8):1949–52.

6. Oliver-Williams C, Vassard D, Pinborg A, Schmidt L. Risk of cardiovascular disease for women with polycystic ovary syndrome: results from a national Danish registry cohort study. Eur J Prev Cardiol. 2020 Aug 2;2047487320939674.

7. Glintborg D, Hass Rubin K, Nybo M, Abrahamsen B, Andersen M. Morbidity and medicine prescriptions in a nationwide Danish population of patients diagnosed with polycystic ovary syndrome. Eur J Endocrinol. 2015 May;172(5):627–38.

8. Abacioglu OO, Gulumsek E, Sumbul H, Kaplan M, Yavuz F. Aumento da Rigidez Arterial Pulmonar e Comprometimento do Acoplamento Ventrículo Direito-Artéria Pulmonar na SOP. Arq Bras Cardiol. 2021; 116(4):806-811.

9. Talbott EO, Guzick DS, Sutton-Tyrrell K, McHugh-Pemu KP, Zborowski JV, Remsberg KE, et al. Evidence for association between polycystic ovary syndrome and premature carotid atherosclerosis in middle-aged women. Arterioscler Thromb Vasc Biol. 2000 Nov;20(11):2414–21.

10. Burger CD, Foreman AJ, Miller DP, Safford RE, McGoon MD, Badesch DB. Comparison of body habitus in patients with pulmonary arterial hypertension enrolled in the Registry to Evaluate Early and Long-term PAH Disease Management with normative values from the National Health and Nutrition Examination Survey. Mayo Clin Proc. 2011 Feb;86(2):105–12.

11. Reddy YNV, Anantha-Narayanan M, Obokata M, Koepp KE, Erwin P, Carter RE, et al. Hemodynamic Effects of Weight Loss in Obesity: A Systematic Review and Meta-Analysis. JACC Heart Fail. 2019 Aug;7(8):678–87.

12. Reddy YNV, Rikhi A, Obokata M, Shah SJ, Lewis GD, AbouEzzedine OF, et al. Quality of life in heart failure with preserved ejection fraction: importance of obesity, functional capacity, and physical inactivity. Eur J Heart Fail. 2020 Jun;22(6):1009–18.

13. Obokata M, Reddy YNV, Pislaru SV, Melenovsky V, Borlaug BA. Evidence Supporting the Existence of a Distinct Obese Phenotype of Heart Failure With Preserved Ejection Fraction. Circulation. 2017 Jul 4;136(1):6–19.

14. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. Circulation. 2018 Aug 28;138(9):861–70.

15. Obokata M, Kane GC, Reddy YNV, Olson TP, Melenovsky V, Borlaug BA. Role of Diastolic Stress Testing in the Evaluation for Heart Failure With Preserved Ejection Fraction: A Simultaneous Invasive-Echocardiographic Study. Circulation. 2017 Feb 28;135(9):825–38.

16. Obokata M, Reddy YNV, Melenovsky V, Pislaru S, Borlaug BA. Deterioration in right ventricular structure and function over time in patients with heart failure and preserved ejection fraction. Eur Heart J. 2019 Feb 21;40(8):689–97.

17. Sorimachi H, Obokata M, Takahashi N, Reddy YNV, Jain CC, Verbrugge FH, et al. Pathophysiologic importance of visceral adipose tissue in women with heart failure and preserved ejection fraction. Eur Heart J. 2020 Nov 23.

Dysautonomia: A Forgotten Condition — Part 1

Eduardo Arrais Rocha,[1] Niraj Mehta,[2,3] Maria Zildany Pinheiro Távora-Mehta,[2,3] Camila Ferreira Roncari,[4] Alan Alves de Lima Cidrão,[5] Jorge Elias Neto[6]

Hospital Universitário Walter Cantídio da Universidade Federal do Ceará (UFC) - Programa de Pós-graduação em Ciências Cardiovasculares da Faculdade de Medicina da UFC,[1] Fortaleza, CE - Brazil
Universidade Federal do Paraná, Curitiba,[2] PR - Brazil
Clínica de Eletrofisiologia do Paraná,[3] Curitiba, PR - Brazil
Departamento de Fisiologia e Farmacologia - Faculdade de Medicina da Universidade Federal do Ceará (UFC),[4] Fortaleza, CE - Brazil
Programa de Pós-graduação em Ciências Cardiovasculares da Faculdade de Medicina da UFC,[5] Fortaleza, CE - Brazil
Serviço de Eletrofisiologia do Vitória Apart Hospital,[6] Vitória, ES - Brazil

Clinical Series of the Brazilian Society of Cardiac Arrhythmias

Abstract — Key Points

Dysautonomia covers a range of clinical conditions with different characteristics and prognoses. They are classified as Reflex Syndromes, Postural Orthostatic Tachycardia Syndrome (POTS), Chronic Fatigue Syndrome, Neurogenic Orthostatic Hypotension (nOH) and Carotid Sinus Hypersensitivity Syndrome. Reflex (vasovagal) syndromes will not be discussed in this article.

1. Reflex (vasovagal) syndromes are mostly benign and usually occur in patients without an intrinsic autonomic nervous system (ANS) or heart disease. Therefore, they are usually studied separately.

2. Cardiovascular Autonomic Neuropathy (CAN) is the term most currently used to define dysautonomia with impairment of the sympathetic and/or parasympathetic cardiovascular autonomic nervous system. It can be idiopathic, such as multisystemic atrophy or pure autonomic failure, or secondary to systemic pathologies such as diabetes mellitus, neurodegenerative diseases, Parkinson's disease, dementia syndromes, chronic renal failure, amyloidosis and it may also occur in the elderly.

3. The presence of Cardiovascular Autonomic Neuropathy (CAN) implies greater severity and worse prognosis in various clinical situations.

4. Detection of Orthostatic Hypotension (OH) is a late sign and means greater severity in the context of dysautonomia, defined as Neurogenic Orthostatic Hypotension (nOH). It must be differentiated from hypotension due to hypovolemia or medications, called non-neurogenic orthostatic hypotension (nnOH).

Keywords

Dysautonomia; Syncope; Hypotension Orthostatic; Chronic Fatigue Disease; Amyloidosis; Chagas Disease; COVID-19; Cardiovascular Autonomic Neuropathy; Carotid Sinus Hipersensitivity; Diabetes mellitus

Mailing Address: Eduardo Arrais Rocha •
Av. Padre Antônio Tomás, 3535/ 1301. Postal Code 60190-120, Fortaleza, CE - Brazil
E-mail: eduardoarraisrocha@gmail.com
Manuscript received May 04, 2020, revised manuscript August 29, 2020, accepted September 09, 2020

DOI: https://doi.org/10.36660/abc.20200420

5. OH can result from benign causes, such as acute, chronic hypovolemia or use of various drugs. However, these drugs may only reveal subclinical pictures of Dysautonomia. All drugs of patients with dysautonomic conditions should be reevaluated.

6. Precise diagnosis of CAN and the investigation of the involvement of other organs or systems is extremely important in the clinical suspicion of pandysautonomia.

7. In diabetics, in addition to age and time of disease, other factors are associated with a higher incidence of CAN, such poor glycemic control, hypertension, dyslipidemia and obesity. Among diabetic patients, 38–44% can develop Dysautonomia, with prognostic implications and higher cardiovascular mortality. In the initial stages of DM, autonomic dysfunction involves the parasympathetic system, then the sympathetic system and, later on, it presents as orthostatic hypotension.

8. Valsalva, Respiratory and Orthostatic tests (30:15) are the gold standard methods for the diagnosis of CAN. They can be associated with RR Variability tests in the time domain, and mainly in the frequency domain, to increase the sensitivity (protocol of the 7 tests). These tests can detect initial or subclinical abnormalities and assess severity and prognosis.

9. The Tilt Test should not be the test of choice for investigating CAN at an early stage, as it detects cases at more advanced stages. Tilt response with a dysautonomic pattern (gradual drop in blood pressure without increasing heart rate) may suggest CAN.

10. Treatment of patients at moderate to advanced stages of dysautonomia is quite complex and often refractory, requiring specialized and multidisciplinary evaluation. There is no cure for most types of Dysautonomia at a late stage.

11. NOH patients can progress with supine hypertension in more than 50% of the cases, representing a major therapeutic challenge. The immediate risk and consequences of OH should take precedence over the later risks of supine hypertension and values greater than 160/90 mmHg are tolerable. Sleeping with the head elevated (20–30 cm), not getting up at night, taking short-acting antihypertensive drugs for more severe cases, such as losartan, captopril, clonidine or nitrate patches, may be necessary and effective in some cases.

12. Preventive measures such as postural care; good hydration; higher salt intake; use of compression stockings and abdominal straps; portioned meals; supervised physical activity, mainly sitting, lying down or exercising in the water are important treatment steps.

13. Various drugs can be used for symptomatic nOH, especially fludrocortisone, midodrine and droxidopa, the latter not available in Brazil. The risk of exacerbation or triggering supine hypertension should be considered.

14. Chronic Fatigue Syndrome represents a form of Dysautonomia and has been renamed as a systemic disease of exercise intolerance, with new diagnostic criteria: 1 - Unexplained fatigue, leading to occupational disability for more than 6 months; 2 - Feeling ill after exercising; 3 - Non-restorative sleep; 4 - One of the following findings: cognitive impairment or orthostatic intolerance. Several pathologies today have evolved with chronic fatigue, being called chronic diseases associated with chronic fatigue.

15. Postural orthostatic tachycardia syndrome (POTS), another form of presentation of dysautonomic syndromes, is characterized by sustained elevation of heart rate (HR) ≥30 bpm (≥40 bpm if <20 years) or HR ≥120 bpm, in the first 10 minutes in an orthostatic position or during the tilt test, without classical orthostatic hypotension associated. A slight decrease in blood pressure may occur. Symptoms appear or get worse in an orthostatic position, with dizziness, weakness, pre-syncope, palpitations, and other systemic symptoms being common.

Vasovagal Syndromes x Dysautonomia

Vasovagal syndromes are clinical situations that are different from cardiovascular autonomic neuropathies, as they do not represent intrinsic diseases in the Autonomic Nervous System (ANS), resulting from reflex, transient, benign mechanisms, therefore having a favorable prognosis.

Dysautonomia: A frequent and underdiagnosed condition

The autonomic nervous system (ANS) regulates important functions in various organic systems such as cardiovascular, digestive, genital-urinary and sudomotor systems. Its dysfunctions can determine several clinical manifestations, some of which are debilitating and serious. Various pathologies can compromise the ANS and determine symptoms, increasing the risk of syncope, falls and higher cardiovascular mortality. Due to the different clinical manifestations and the poor familiarity of professionals, Dysautonomia is often underdiagnosed, being recognized at more advanced stages, with debilitating and incapacitating symptoms and worse prognosis.

The term cardiovascular autonomic neuropathy (CAN) means involvement of the autonomic nervous system, related to cardiovascular functions. Diabetes mellitus (DM) represents the most common and studied form of CAN and serves as a model for understanding and investigating several other pathologies.[1,2]

In the diabetic population, it is known as Diabetic Cardiovascular Autonomic Neuropathy, with a prevalence of 20% in patients with DM, up to 54% in type 1 (DM1) and 46% in type 2 (DM2), between 40 and 70 years. In diabetics, in addition to age and time of disease, other factors are associated with a greater risk of CAN, such as poor glycemic control, hypertension, dyslipidemia and obesity. In the initial stages of DM, autonomic dysfunction involves the parasympathetic system, then the sympathetic system and, later, it evolves to orthostatic hypotension.

The cardiovascular autonomic nervous system modulates heart rate, diastolic and systolic volumes, QT interval and systemic vascular resistance. Its impairment is related to increased cardiovascular morbidity and mortality.

The purpose of this review is to provide relevant information on the different forms of autonomic dysfunctions, their clinical manifestations, diagnostic and therapeutic methodologies, and prognostic implications. We emphasize the importance of diagnosis, of its distinction with vasovagal reflex syndromes and the need for greater dissemination of information on these pathologies, since it is little remembered in general clinical practice. Reflex vasovagal syndromes will not be addressed in this chapter.

Various guidelines were considered in this review, including: Cardiovascular Autonomic Neuropathy (CAN) Guidelines, Consensus Statement on Neurogenic Orthostatic Hypotension and Supine Hypertension, Syncope Guidelines, Guidelines on CAN in Diabetics, Guidelines on Cardiovascular Tests in Autonomic Neuropathy, Consensus Statement on the Investigation of Autonomic Dysfunction in Human Research Studies, Consensus Statement on the Diagnosis and Treatment of Postural Orthostatic Tachycardia Syndrome and Inappropriate Sinus Tachycardia, and other studies. Discussions between specialists of the Brazilian Society of Cardiac Arrhythmias were included, considering the lack of major studies on various topics covered in this study.[1-20]

Physiology of the Autonomic Nervous System

The autonomic nervous system (ANS) plays an important role in the control of visceral functions through the sympathetic and parasympathetic subdivisions.

The ANS provides neurovegetative adjustments for the expression of motivated behaviors or compensatory responses to internal and external stimuli in order to promote the maintenance of homeostasis, along with the endocrine system. The term "autonomic nervous system" was proposed by Langley, in 1898, as the nomenclature used until then had different connotations and were inaccurate as to the recently discovered functions of this system.[20]

For easier comprehension the ANS is commonly analyzed for its anatomical, neurochemical and functional aspects. The basic organization involves two neuronal groups arranged in series and connected by a chemical synapse. The second neuron in this series is completely outside the central nervous system and its cellular body is located in the autonomic ganglia, from where axonal projections come out, which will innervate the target organs; hence their denomination as postganglionic neurons.[21]

The neurons that send axonal which send axonal projections from the central nervous system to the ganglia, making synapse with the cellular bodies present in these structures are called preganglionic neurons.

The anatomical difference between sympathetic and parasympathetic ANS concerns the location of the cellular bodies of preganglionic neurons. Sympathetic preganglionic neurons are located in thoracic and lumbar segments of the spinal cord and the parasympathetic ones are located in the brain stem and in the sacral segments of the spinal cord.

Regarding neurochemistry, all preganglionic neurons are cholinergic and use acetylcholine as a neurotransmitter.

Despite some exceptions, parasympathetic postganglionic neurons release acetylcholine in the target organ, while sympathetic postganglionic neurons release noradrenaline.

The adrenal medullary cells are homologous to the sympathetic postganglionic neurons nd primarily secrete adrenaline and, to a lesser extent, norepinephrine directly into the bloodstream, in response to stimulation by sympathetic preganglionic neurons.

Finally, the sympathetic and parasympathetic nervous systems differ as to the responses triggered in the target organs. A few structures receive single innervation, while most organs receive double innervation. The responses induced by sympathetic and parasympathetic ANS stimulation can be antagonistic or cooperative.

As shown in figure 1, systemic blood vessels are innervated by sympathetic ANS. Greater activation of α_1-adrenergic receptors through increased sympathetic tone or adrenaline release by the adrenal gland causes vasoconstriction in most systemic blood vessels, especially in the vessels of the abdominal viscera, an important vascular resistance bed with great influence on the determination of blood pressure (BP).

In contrast, reduced sympathetic tone or plasma levels of adrenaline results in vasodilation. Coronary blood vessels particularly express β_2 receptors and undergo vasodilation in response to adrenaline.

The heart is innervated by the sympathetic and parasympathetic systems (Figure 1). Cardiac parasympathetic innervation is directed to the sinoatrial (SA) and atrioventricular (AV) nodes and acetylcholine binds to the M2 muscarinic acetylcholine receptors expressed in the nodal cells, inducing a negative chronotropic effect. On the other hand, sympathetic ANS innervates both the SA and AV nodes, as well as the ventricular muscle. Noradrenaline induces positive chronotropic and inotropic effects by acting on β_1-adrenergic receptors.[22]

All cardiac cells, in principle, have the electrical property of automatism; however, under physiological conditions, SA nodal cells present spontaneous depolarization in a higher frequency and take control of the heartbeat, and are thus considered the cardiac pacemaker.

Upon pharmacological blockade of muscarinic and β-adrenergic receptors, the intrinsic heart rate generated by the sinoatrial node is approximately 100 beats per minute, suggesting that there is a predominance of parasympathetic influence on the heart.[23] For BP adjustments, the sympathetic and parasympathetic tone for the heart and blood vessels are often modified by the baroreflex.

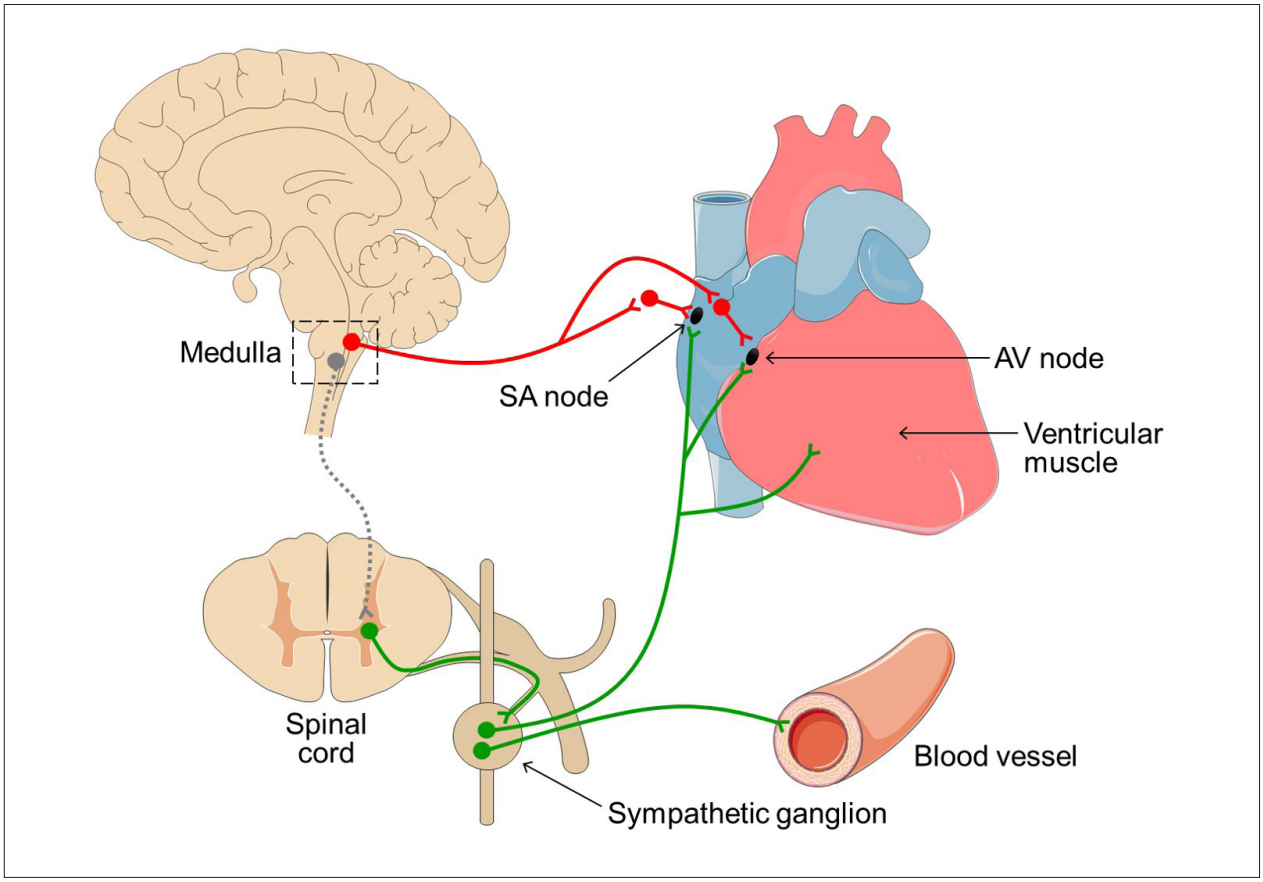


Figure 1 – *Schematic representation of heart and blood vessels innervation by the sympathetic and parasympathetic ANS. Parasympathetic neurons are represented in red and sympathetic neurons are represented in green. SA node — sinoatrial node; AV node — atrioventricular node. For better viewing, a single schematic spinal segment was represented and the images are not represented on the same graphic scale.*

Blood pressure (BP) is constantly monitored by high-pressure baroreceptors (stretch receptors) found in the aortic arch and carotid sinus, which send signaling through the vagus and glossopharyngeal nerve, respectively, to the nucleus of the solitary tract (NTS), located in the dorsomedial portion of the medulla.[24]

When BP is high, the baroreceptors are more activated and, by baroreflex mechanisms, there is an increase in parasympathetic tone and a reduction in sympathetic tone to the heart and blood vessels. Increased baroreceptor firing rate activates the NTS, which in turn activates the nucleus ambiguus (NA), the bulbar nucleus where the parasympathetic preganglionic neurons cellular bodies are located, resulting in an increase in parasympathetic tone. In parallel, the NTS also activates the caudal ventrolateral medulla (CVLM), which sends inhibitory projections to the rostral ventrolateral medulla (RVLM). RVLM neurons are considered pre-sympathetic, because they project into the spinal cord intermediolateral cell column and synapse with the cellular bodies of sympathetic preganglionic neurons. Therefore, the greater activity of CVLM results in inhibition of RVLM and, consequently, reduction of sympathetic tone.

On the other hand, the lower activity of baroreceptors when BP is decreased results in: 1) less NA activation and, therefore, reduction of parasympathetic tone; and 2) less CVLM activation and, consequently, greater RVLM activity and increased sympathetic tone to the heart and blood vessels.

Changes in the normal functioning of the baroreflex mechanism can trigger pathological conditions called dysautonomia, such as neurogenic orthostatic hypotension, for example. The change from the supine to the orthostatic position increases the gravitational resistance to venous return, resulting in decreased end diastolic volume and, consequently, systolic volume (SV), observed in several pathologies.

BP is directly proportional to total peripheral resistance and cardiac output, the latter being the volume of blood pumped by the heart per minute, that is, SV multiplied by heart rate (HR).

Thus, reduced SV on switching to the orthostatic position induces hypotension. In healthy individuals, this hypotension is transient as the baroreflex mechanisms are quickly activated and cause an increase in contractile force and HR and systemic vasoconstriction, compensatory responses that normalize BP. In individuals with dysautonomia, prolonged hypotension called neurogenic orthostatic hypotension (nOH), may occur.

Multiple system atrophy (MSA) — Shy-Dragger syndrome

The complete syndrome consists of orthostatic hypotension, bladder and bowel incontinence, loss of sweating, iris atrophy, external eye paralysis, stiffness, tremors, loss of movement, impotence, fasciculations, distal muscle atrophy and evidence of neuropathic lesions. The onset is usually is the 5th–7th decade of life.

Pathophysiology and clinical presentations

Various pathophysiological mechanisms have been described in autonomic nervous system (ANS) abnormalities. They may vary depending on specific etiologies, such as diabetes or amyloidosis. Several situations, however, have their causal mechanisms unknown.

Although other neurotransmitters are important in the regulation of cardiovascular responses, the release of noradrenaline in sympathetic postganglionic nerve endings is the most important mediator of the rapid cardiovascular regulation required in blood pressure balance and cerebral perfusion. Neurogenic orthostatic hypotension represents a deficiency in the responsiveness of this neurotransmitter to postural change.

Unlike reflex or vasovagal syndromes, in dysautonomia conditions, the reflexes of increased heart rate preceding the clinical picture and bradycardia concomitant with hypotension are not observed.

In diabetes mellitus, metabolic and vascular abnormalities occur that can justify neurological damage. Hyperglycemia, accumulation of sorbitol, fructose and end products of advanced glycation, with bindings to receptors in the smooth endothelial and muscle cells of vasa nervorum Schwann cells and macrophages may contribute to neurological damage. Oxidative stress leading to depletion of antioxidant cellular enzymes and activation of inflammation cascade, with deterioration of cellular organelles, especially at the mitochondrial level, are other mechanisms that culminate in vascular occlusion, endothelial dysfunction and neuroinflammation, determining toxicity and neuronal death.[25-30]

Sinucleinopathy, a condition that involves Parkinson's Disease, Lewy body dementia, pure autonomic failure (Bradbury and Eggleston syndrome) and multiple system atrophy (Shy and Dragger syndrome), causes intracellular deposition and aggregation of a protein called alpha-synuclein in different areas of the central and peripheral nervous system.[19,31,32]

Multiple system atrophy (MSA),[32] a more severe and rare idiopathic form, described in 1960, comes in two forms: 1. Parkinsonism: muscle stiffness and bradykinesia are observed (it is different from the classical Parkinson's disease, in which tremors prevail) 2. Cerebellar MSA: ataxia symptoms. Both forms have involvement of the autonomic nervous system.[8] Nuclear magnetic resonance imaging of the brain reveal cerebellar, pons or peduncle atrophy, or hypersignal on the pons, known as the hot cross bun sign, which may occur later. Catecholamine dosages are usually normal, as it is a preganglionic autonomic polyneuropathy.

In pure autonomic failure, of idiopathic etiology, described in 1925 and known as postganglionic autonomic polyneuropathy, the symptoms are gradual, progressive, and may involve severe and debilitating conditions, with severe cardiovascular involvement, severe orthostatic hypotension, with involvement of the genitourinary, digestive and sudomotor systems.

Because they do not have central neurodegenerative symptoms, brain imaging tests in pure autonomic failure are normal and plasma catecholamine levels are normal or low, but do not show an adequate increase (>50%) with orthostasis, due to diffuse peripheral sympathetic denervation.

Some toxins can be causal factors, such as lead, thallium or arsenic poisoning, or use of some drugs such as chemotherapy drugs of the cisplatin class or vinca alkaloids, antiarrhythmic

drugs such as amiodarone or vitamin deficiencies such as vitamin B12 deficiency.

Rare cases of family origin may occur, such as Hereditary Sensory and Autonomic Neuropathy (HSAN). These are divided into: Type I HSAN, which is lighter and starts in adult life, with distal sensory and autonomic involvement, and foot ulcers; type II HSAN, rarer, starting in childhood, with more diffuse and severe impairment.[8,19,31,33]

Autoimmune etiologies can justify various acute and subacute clinical presentations of pandysautonomia, with some similarities with Guillain-Barré syndrome (GBS). However, in acute pandysautonomia, somatic fibers are generally spared, unlike GBS. Some degree of autonomic dysfunction is also present in most cases of GBS.[31,34,35]

Amyloidosis

Amyloidosis may occur in the following forms:

1) In the most common form, known as light chain (AL) or primary amyloidosis, there is abnormal clonal proliferation of plasma cells. Initially, peripheral sensitive distal neuropathy progresses to broad fibers, with subsequent autonomic failure of multiple affected organs, such as the digestive system, including esophagus and intestine, sudomotor system with alternating anhidrosis with compensatory sweating, renal involvement and nephrotic syndrome and cardiac involvement, with heart failure, arrhythmia and sudden death. In the autonomic evaluation, impairment of the sympathetic and parasympathetic systems can be found.

2) Familial amyloidosis (FA), also called paramyloidosis or Corino Andrade's disease,[36,37] is found in the autosomal dominant form, originally described by Portuguese professor Dr. Corino de Andrade, in 1952. It has a higher incidence between 20 and 40 years of age, evolving to death at 10–12 years.

It has a variable phenotype, depending on the geographic region and the mutation. Several forms have been described, such as: Portuguese (type I) or Andrade, Rukovina or Indiana (type II), van Alien (type III) and the Finnish type (type IV). In Brazil, some forms of this pathology have been described.[38]

Mutation in the transthyretin (TTR) gene is the best known and studied, with various mutations described in this gen. It begins with symptoms of peripheral neuropathy, which can progress to severe generalized autonomic dysfunction, in addition to cardiological, neurological (sensorimotor peripheral polyneuropathy), visual, genitourinary, renal and gastrointestinal symptoms. Early detection is extremely important, aiming at treatment and preventing progression. Liver transplantation before the disease is advanced can change its course. New promising drugs have been launched, such as Tafamidis (TTR stabilizers), available in Brazil, and Inotersen.

3) The secondary form (AA form) is due to chronic pathologies, such as rheumatoid arthritis, osteomyelitis, tuberculosis, renal failure and its evolution depends on the control of the underlying disease.

Cardiac amyloidosis is mainly caused by AL or transthyretin-type FA (ATTR) or by deposition of wild-type transthyretin protein, once called senile cardiac amyloidosis. TTR deposits were found in 16% of patients with degenerative aortic stenosis and in up to 17% of patients with preserved ejection fraction heart failure. The prognosis after cardiac involvement is poor, with survival ranging from 2.5 to 3.6 years. On significantly increased left ventricular wall thickness (>14 mm), despite its low voltage, electrocardiography may suggest the diagnosis, complemented by cardiac nuclear magnetic resonance imaging and technetium pyrophosphate scintigraphy.[39]

The randomized study ATTR-ACT, evaluating the safety and efficacy of Tafamidis in patients with cardiac amyloidosis, revealed a reduction in all causes of mortality and hospital admissions after 30 months of follow-up, so Tafamidis started to be prescribed in this pathology, for NYHA (New York Heart Association) functional class (FC) I, II and III heart failure, mainly in the early stages. This was the first therapy to show improved survival of these patients.[40]

In many cases of dysautonomia, reports of recent viral infections are identified, especially by herpesviruses, Epstein-Barr and Coxsackie. Autoantibodies to ganglionic acetylcholine receptors (AChr) were found in 50% of patients with PAF, in 7% of patients with POTS and 0% in controls. The absence of these antibodies does not rule out the diagnosis. Case reports have demonstrated therapeutic success with the application of immunoglobulins in some of these clinical situations.[31,34,35,41-43]

In paraneoplastic syndromes, more commonly in small-cell lung carcinomas, the presence of autoantibodies, especially anti-Hu or ANNA-1, is usually present and clinical presentations are usually acute or subacute.

The autoimmune theory is reinforced by the appearance of symptoms after viral conditions, feverish conditions, after vaccination and in patients with previous autoimmune diseases, such as Hashimoto's thyroiditis, celiac disease and systemic lupus erythematosus.

Studies have shown that the autoimmune theory may be the pathophysiological mechanism of the "idiopathic" forms of some dysautonomic syndromes, such as pure autonomic failure (PAF), POTS or chronic fatigue syndrome.[43]

Anti-nicotinic cholinergic receptor antibodies have also been described. Authors have recently demonstrated the mechanism by which autoantibodies cause vasodilation and tachycardia. These findings may have important therapeutic implications. In the presence of anti-acetylcholine antibodies, the use of drugs such as pyridostigmine may be beneficial. In the presence of adrenergic antibodies, beta-blockers could be the best choice.

Chagas Disease

Cardiac dysautonomia is well established in Chagas disease (ChD), in which anatomical denervation and functional abnormalities have been described in in vivo, post-mortem and experimental studies.[44-46] Carlos Chagas' original studies already called attention to the absence of a chronotropic response to atropine in patients with Chagas disease.[47] In addition to denervation, other autonomic nervous system abnormalities, such as ganglionitis, neuritis, fibrosis, atrophy and fragmentation of specialized fibers have also been reported.[48]

Parasympathetic impairment can be detected in all forms of ChD, including the indeterminate and independent phase of left ventricular function.[49,50] These data were corroborated by a meta-analysis that included seven studies that evaluated cardiac autonomic modulation, using R-R variability during the Valsalva maneuver.[51]

Studies with metaiodobenzylguanidine I-$_{123}$ ($_{123}$I-MIBG) have detected indeterminate form sympathetic dysfunction in Chagas disease patients without left ventricular systolic dysfunction.[52,53] $_{123}$I-MIBG scintigraphy was also used to assess the presence and magnitude of sympathetic dysfunction in patients with Chagas cardiomyopathy and ventricular dysfunction (EF≤45%). The authors observed decreased $_{123}$I-MIBG uptake, indicating dysfunction of sympathetic receptors and loss of integrity of the presynaptic sympathetic fibers.[52]

An aspect that requires further clarification is the role of immune-mediated mechanisms in Chagas cardiomyopathy. In fact, many studies have demonstrated the presence of antibodies that react with cardiac muscarinic M2 receptors and B1 adrenergic receptors in the serum of asymptomatic Chagas disease patients.[48,54]

These autoantibodies could play a role in the pathogenesis of Chagas myocarditis, explaining cardiac neuromyopathy, described in the indeterminate phase.

Another topic that is poorly evaluated in Chagas dysautonomia is the investigation of orthostatic hypotension. In the ELSA-Brasil study, patients with positive ChD serology had a greater association with orthostatic hypotension (OR=2.29 — 95% CI: 1.2–4.2).[55] In fact, there are inconsistent results in the evaluation of vascular control in Chagas disease patients (8). In contrast to other disorders with wide ANS involvement (for example, DM and amyloidosis), the presence of orthostatic hypotension in ChD is not usually described.[44,56]

Early autonomic impairment in ChD suggests that cardiovascular dysautonomia may be associated with increased morbidity and mortality, cardiac arrhythmia and sudden death.[49,52] It could be one of the central pillars in several clinical manifestations, such as diastolic and/or systolic dysfunction, ventricular dilation, tachyarrhythmia and bradyarrhythmia and sudden cardiac death.[45,50,53] Cardiac autonomic dysfunction must be a determinant or a predisposing pathophysiological risk factor in the genesis of arrhythmia. Greater arrhythmogenic vulnerability is observed in cases with more focal autonomic dysfunctions than in cases with more diffuse and significant injuries, due to a greater degree of central nervous system disconnection, with less susceptibility to ANS interference in cardiac electrophysiological properties.[45,57]

The observation of sustained ventricular tachycardia in patients with Chagas cardiomyopathy, with preserved ventricular function and regional myocardial sympathetic denervation (detected by $_{123}$I-MIBG scintigraphy), as well as during orthostatic stress in a patient with mild impairment of ventricular function and no significant baseline electrocardiographic abnormalities lead to an alleged role of autonomic dysfunction in the pathophysiology of rhythm disorders in Chagas cardiomyopathy.[53]

Orthostatic Hypotension — A Sign of Late Stage and Severity

The detection of neurogenic orthostatic hypotension (nOH) usually represents a late stage and severity, correlated with worse prognosis. Therefore, one should not wait for its presence for diagnosis of dysautonomia. Patients with known pathologies or symptoms that compromise the ANS should be investigated early.

Classification of Clinical Syndromes

Cardiovascular Autonomic Neuropathy (CAN)

CAN is a term widely used by the Societies of Diabetes and Autonomic Neuropathy to express impairment of the cardiovascular autonomic nervous system in the presence of diabetes mellitus, but the term is not restricted to this pathology.[7] CAN includes ANS involvement, from the pre-clinical stage, which may have prognostic implications, such as glucose intolerance or pre-diabetes. (Figura 2)

The expression neurogenic orthostatic hypotension, widely used by arrhythmologists and cardiologists, links the need for the presence of OH to define the diagnosis, a situation that, when detected, may represent a late and more severe stage, often with irreversibility of the condition.

Neurogenic Orthostatic Hypotension (nOH) and Supine Hypertension

Orthostatic hypotension is defined by the presence of reduced systolic blood pressure (BP) of at least 20 mmHg or diastolic BP of 10 mmHg or both, within 3 minutes after active orthostatic position or during the tilt test.[3]

In patients with nOH, impairment of the autonomic nervous system is observed, characterized by the inability to provide adequate vasoconstriction and/or adequate compensatory increase in heart rate (HR), sufficient to maintain BP in an orthostatic position. In most cases, this dysfunction is attributed to the insufficient release of norepinephrine from the sympathetic nerves.[42,43]

While in nOH impaired vasoconstriction is due to permanent damage in the efferent sympathetic activity, in non-neurogenic orthostatic hypotension (nnOH), it includes a variety of causes, such as the use of medications, antihypertensives, antidepressants, and alpha-blocking agents (Table 1), in addition to volume depletion and chronic diseases that lead to physical deconditioning.[58]

It is important to differentiate nOH from nnOH due to the worse prognosis of nOH, with greater morbidity and mortality from all causes. Furthermore, studies point out that the presence of OH in middle-aged individuals predisposes to myocardial hypertrophy even in the absence of hypertension.[58,59] The incidence of OH increases with age, as well as hypertension, diabetes and cardiovascular or degenerative diseases.[42,43,59]

Patients with one of the five categories below are at increased risk for nOH compared to the general population and should be routinely investigated (Figure 3):

1. Suspected or diagnosed with any degenerative disease associated with autonomic dysfunction, including

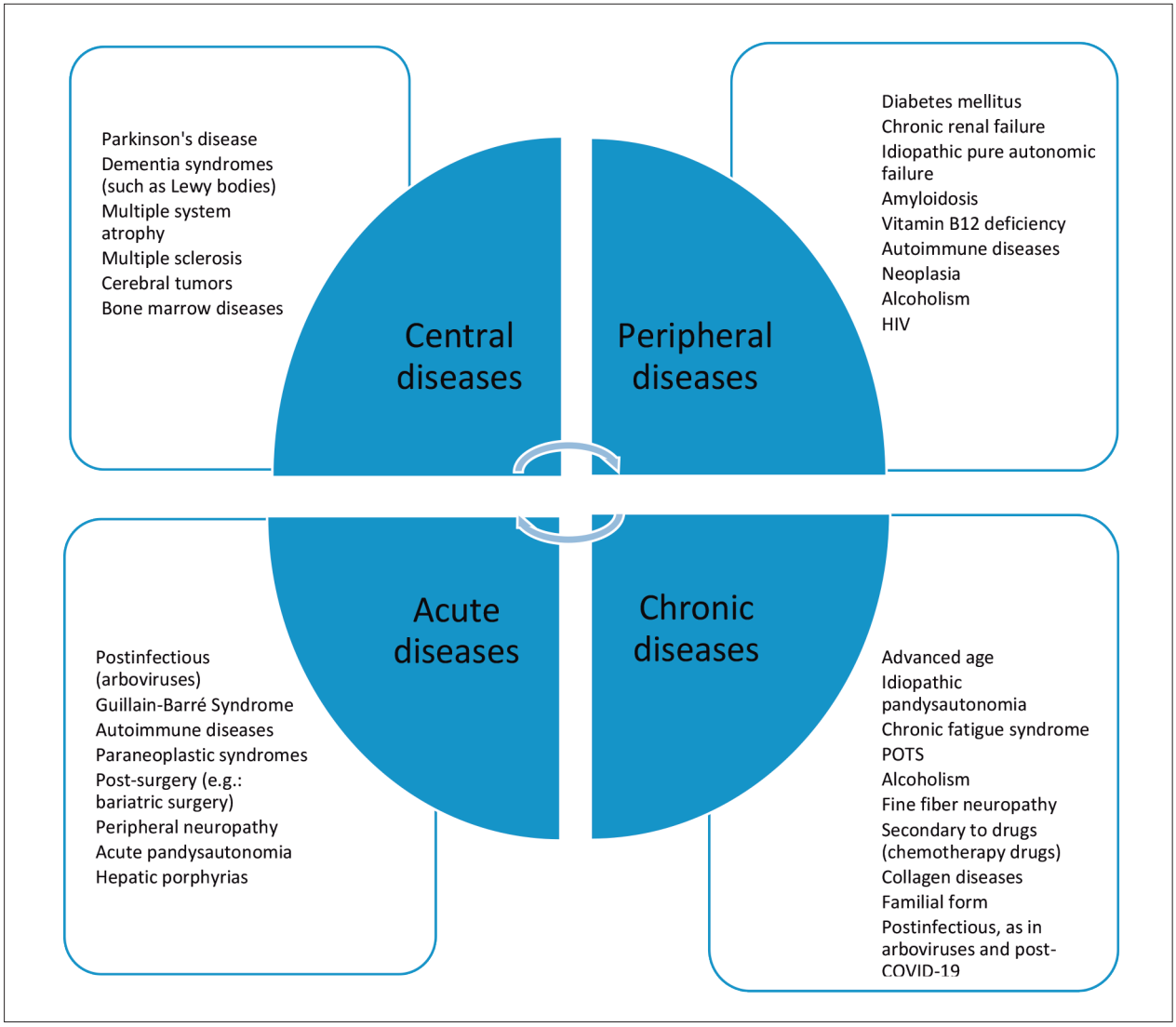


Figure 2 – *Causes of dysautonomia. Source: prepared by the author. The image includes examples as different causes of acute or chronic, central or peripheral autonomic dysfunctions. Some pathologies can present in different ways. POTS: Postural orthostatic tachycardia syndrome.*

Parkinson's disease, multiple system atrophy, pure autonomic failure or dementia by Lewy bodies;

2. History of unexplained falls or syncope;

3. Presence of peripheral neuropathy;

4. Age ≥70 with a high degree of fragility or use of multiple medications;

5. Dizziness or unspecific orthostatic symptoms.

After identifying that a patient is at risk for orthostatic hypotension, it is important to measure BP and HR in the supine position (after 5 minutes lying down) and in the first and third minutes after the orthostatic position, which is considered the gold standard for OH diagnosis.[58] These values must also be measured after 5 minutes of orthostasis.

An alternative method would be taking these measurements after the patient has been 5 minutes in the sitting position, then after 3 minutes in the orthostatic position. Many of these patients still have supine hypertension (systolic BP ≥140 mmHg and/or diastolic BP≥90 mm Hg). In this situation, it is recommended to consider OH if there is a drop in systolic BP≥30 mmHg and/or diastolic BP≥10 mmHg.[58]

HR measurements also vary from supine position (and/or sitting position) to orthostatic position and help to differentiate nOH from nnOH.[42,59] In individuals with OH, a compensatory HR increase of at least 15 bpm is expected within 3 minutes in the standing position. If this does not occur, OH is possibly neurogenic (as long as there is no concomitant use of negative chronotropic medication or conduction system disease or patient with a pacemaker).

A review of the prescribed drugs should be carried out in order to avoid effects on the baroreflex response (table 1), especially alpha- and beta-adrenergic blockers and centrally acting alpha-2 agonists.

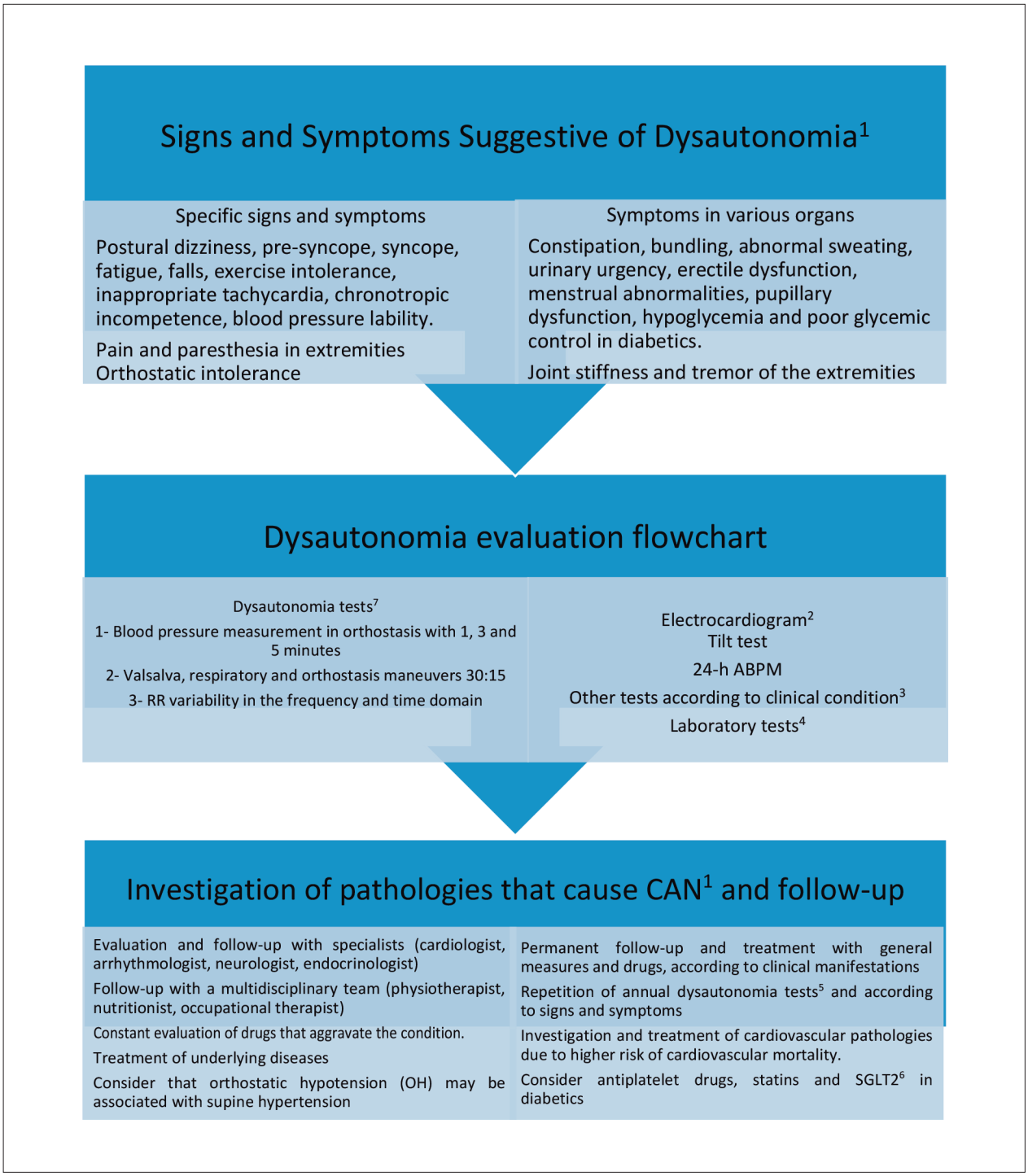


Figure 3 – *Flowchart of Evaluation and Follow-up of Dysautonomia or Cardiovascular Autonomic Neuropathy (CAN) Source: prepared by the author.*
1. It occurs idiopathically, as in multiple system atrophy or pure autonomic failure, or in pathologies such as diabetes mellitus, neurodegenerative diseases, Parkinson's disease, dementia syndromes, chronic renal failure, amyloidosis, some neoplastic diseases and in the elderly.
2. Electrocardiogram to assess heart rate and QT interval.
3. Neurological tests such as electromyography, brain resonance imaging, cardiological tests such as 24-h Holter, ischemia evaluation.
4. Laboratory tests including complete blood count, renal function, cortisol, ACTH, glycemic profile, plasma catecholamines collected lying down and immediately after orthostasis, neoplastic and autoimmune disease markers, and others (see specific section).
5. As recommended by international guidelines on diabetics.[1,2,7]
6. SGLT2 — Diabetes medications — sodium-glucose co-transporter inhibitors used to treat diabetes
7. Patients with very frequent extrasystoles, atrial fibrillation, cardiac pacemaker and advanced cognitive dysfunction cannot be evaluated using this methodology. Consider that several drugs must be suspended for the examination and the values of the measurements must be correlated with normal values for age and sex.

Table 1 - Medications that can cause orthostatic hypotension or exacerbate symptoms of neurogenic orthostatic hypotension

Class of medications	Examples
Dopaminergic drugs	Levodopa, dopamine agonists
Tricyclic antidepressants	Amitriptyline, nortriptyline
Anticholinergics	Atropine
↓ Pre-load Diuretics	Furosemide, hydrochlorothiazide, spironolactone
Nitrates	Isosorbide dinitrate
Phosphodiesterase inhibitors	Sildenafil, vardenafil
Vasodilators Alpha-1 adrenergic antagonists Ca++ blockers Direct vasodilators	Doxazosin, tamsulosin Amlodipine, nifedipine Hydralazine
Negative inotropes and chronotropics Beta-blockers	Propranolol, metoprolol, atenolol, bisoprolol, nebivolol, carvedilol
Non-dihydropyridine calcium channel blockers	Diltiazem, verapamil
Central action sympatholytics	Clonidine, methyldopa
Renin-angiotensin system antagonists Converting enzyme inhibitor Angiotensin blockers	Captopril, enalapril, perindopril Losartan, telmisartan, candesartan

Source: Adapted[4]

Some patients may have postprandial hypotension, particularly after large meals rich in carbohydrates, combined with alcoholic beverages. In these conditions, BP measurements in the supine and orthostatic position should be performed before and after the meal, which can usually occur up to 90 minutes after the meal.

Symptoms of orthostatic intolerance may occur in patients without orthostatic hypotension detectable on clinical examination due to impaired peripheral vasoreactivity and venous return. In these cases, reduced stroke volume is observed during hemodynamic monitoring in the orthostatic tilt test. The compensatory HR response is sufficient to maintain blood pressure at acceptable levels.[59,60]

Complementary investigation (table 2) is applied to uncover potential non-neurogenic causes of OH.[58]

If the standardized blood pressure measurements for the diagnosis of OH are not effective for the diagnosis, other approaches can be taken:

1. Advise the patient to measure BP and HR at home in different situations:

a. Fifteen minutes after going to bed at night or before getting up in the morning;

b. Three minutes after taking an orthostatic position, before taking medication or whenever symptoms appear;

2. Perform the orthostatic tilt test, which can document an early or late OH;

3. Perform 24-hour ambulatory blood pressure monitoring (ABPM) — the patient should take notes on lying down and getting up.

When diagnosis of OH is confirmed, it is important to establish the severity, which depends on the magnitude of the drop in systolic BP, the time of tolerance in the orthostatic position and the magnitude of the symptoms to daily activities.

A grading scale from 1 to 4 (table 3) was proposed as a stratification of these patients. For grades 3 and 4, it is advisable to refer the patient to a center specializing in the treatment of orthostatic hypotension.[61]

Orthostatic hypotension may be present in only 30–50% of patients with pure autonomic failure and in 60–70% with multiple system atrophy.[33]

Pandysautonomia and Evaluation Scores

Many pathologies can promote the global involvement of the ANS, with impairment of various systems and organs.

It is called pandysautonomia when there is evidence of systemic dysautonomia: cardiovascular dysautonomia and dysautonomia of various organs. Patients with cardiovascular autonomic neuropathy and/or neurogenic orthostatic hypotension should be asked about specific symptoms in other systems.

Some questionnaires can be used for better clinical evaluation, such as the ASP (Autonomic Symptom Profile), which contains 73 questions and the COMPASS (Composite Autonomic Symptom Scale), which uses the previous scale and quantifies the severity of abnormalities. Validation of these questionnaires has not been done in different clinical contexts. However, the items that comprise it can be used as a screening tool in the suspicion of impairment of other organs. [61,62]

More recently, a new Survey of Autonomic Symptoms (SAS) score was developed and validated, showing better sensitivity

Table 2 – Investigation of patients with orthostatic hypotension (OH)

Diagnostic tests	
Electrocardiography	Evaluate rhythm and conduction disorders, hypertrophy, low voltage
Complete blood count	Evaluate anemia and/or infection
Metabolic profile (sodium, potassium, calcium, creatinine, urea, fasting glucose, glycated hemoglobin, bicarbonate); Urinary sodium in 24 hours	Volume depletion (urea/creatinine ratio >20 mg/dl; kidney failure or diabetes or metabolic disorders
TSH, free T4, Cortisol, ACTH, vitamin B12	Thyroid and adrenal dysfunction and vitamin B12 deficiency
Serum albumin	Malnutrition and chronic disease
Enzymes and liver function	In patients with weight loss, suspected alcoholism
Study of autoantibodies (ANNA-1; ANNA-2, Anti-AChr, LGI1, and others) in cerebrospinal fluid and/or blood	Recent onset OH, suspected paraneoplastic syndrome, pure autoimmune autonomic failure
Serum and urinary protein electrophoresis, protein immunofixation Nerve biopsy, abdominal fat with Congo red stain	In patients with peripheral neuropathy, suspected amyloidosis
Plasma catecholamines in decubitus and after orthostasis	Pure autonomic failure
Serology for arboviruses (dengue fever), for COVID-19, HIV serology	Investigation according to clinical history
Investigation for collagenoses (autoantibodies such as FAN, anti-DNA, anti-SM, Anti-RNP)	Suspected collagenoses

Source: Adapted;[58] Anti-AChR: Autoantibodies to ganglionic acetylcholine receptors (AChR); ANNA: anti-neuronal nuclear antibodies; anti-RNP: anti-ribonucleoprotein antibodies; HIV: acquired immunodeficiency virus. COVID-19: Infection with the new coronavirus has been associated with dysautonomic forms such as the chronic fatigue syndrome.

Table 3 – Grading scale for the severity of neurogenic orthostatic hypotension

Grade	Signs and symptoms
1	Infrequent symptoms/no restriction to stand upright, with 20 to 30 mm Hg drop in SBP
2	>30 mmHg drop in SBP upon orthostasis time ≥5 min
3	>30 mmHg drop in SBP upon orthostasis time <5 min or severe impact on daily activities
4	>30 mm Hg drop in SBP in <1 min in orthostasis or functional incapacity.

Source: Adapted.[61]

in detecting mild autonomic neuropathies, not requiring complementary methods, and it can be a good clinical tool for early detection of autonomic neuropathy (Table 4).[61]

Chronic Fatigue Syndrome

It is currently considered a chronic systemic disease that profoundly affects the quality of life of patients. It has been called chronic fatigue or myalgic encephalomyelitis due to the documentation of central and autonomic nervous system abnormalities. This syndrome affects about 2.5 million individuals of all ages in the USA and dramatically reduces productive capacity.

It is a complex disease that involves deregulation of the central nervous system, the immune system, with dysfunction of the cellular energy metabolism and ionic transport, in addition to cardiovascular abnormalities. It is characterized by persistent and recurrent fatigue after exercise, with no other cause that explains the origin of the symptoms (table 5).[9,63-66]

Routine laboratory tests are usually normal. Impaired autonomic regulation of the vascular system is commonly found, especially in deficient response to orthostatic position, resulting in high association with dysautonomia (figures 4 and 5).

Neuroinflammation can have different triggering factors: brain infection (chronic herpes virus), autoantibodies, neurotoxins or chronic stress, and extra-cerebral inflammatory processes, including the intestine. Low levels of neuroinflammation trigger protective behavioral abnormalities, such as reduced activity, reduced appetite and increased sleep.[63-66]

Functional magnetic resonance imaging in patients with chronic fatigue demonstrated different responses to visual and auditory stimuli and memory tests, as well as abnormalities in connectivity between areas of the brain. Positron emission tomography demonstrated widespread neuroinflammation and high lactate levels, which correlate with degrees of fatigue. In the spinal fluid, there is a higher rate of proteins related to injury and muscle repair.[65,66]

Metabolic abnormalities have also been described, resulting in impaired generation of cellular energy from different sources: oxygen, sugar, lipids and amino acids, with high levels of oxidative stress and nitric acid. Many metabolites are found to be below normal levels. This hypometabolic condition is observed in some animals in hibernation and allows animals under threat to slow down the metabolic process of energy consumption to preserve vital functions.[65,66]

Table 4 – Survey of Autonomic Symptoms (SAS) questionnaire to diagnose the involvement of different organs and systems in dysautonomia

Symptoms/Health Problem	Have you had any of these symptoms in the last 6 months? 1- Yes; 2- No	How severe is this symptom? Scale of 1 to 5 (used if symptoms are present)
1-Darkened vision?	1 or 2	1 – 5
2-Dry mouth or dry eyes?		
3-Pallor or cyanosis?		
4-Feeling cold in some regions of the body?		
5-Reduced feet sweating compared to the rest of the body?		
6-Reduced or absent feet sweating after exercising or in hot weather?		
7-Increased hand sweating compared to the rest of the body?		
8-Nausea, vomiting or gas after light meals?		
9-Diarrhea (>3 bowel movements per day)?		
10-Persistent constipation?		
11-Loss of urine?		
12-Erection issues?		

Source: Adapted.[61] The presence of 3 or more symptoms resulted in 95% sensitivity and 65% specificity, while the presence of 7 or more points determined 60% sensitivity and 90% specificity. Gastrointestinal symptoms were less correlated with other indexes.

Table 5 – Classical Criteria for the Diagnosis of Chronic Fatigue Syndrome

Extreme, persistent or recurrent tiredness, without a justified cause, with the following characteristics:
1. Recent onset (that is, non-progressive throughout life) or with specific trigger
2. Difficulty performing usual professional, physical or social activities
3. Meeting at least 4 of the following criteria:
3.1. Impaired concentration and recent memory
3.2. Sore throat
3.3. Cervical or axillary lymph nodes
3.4. Joint and muscle pain
3.5. Headache
3.6. Non-restorative sleep
3.7. Post-exertional malaise persisting for >24 hours

Source: Adapted[9]

Abnormalities of the autonomic nervous system include abnormal heart rate and blood pressure during prolonged orthostatic position, which are not sufficient to deliver diagnosis of POTS, or orthostatic hypotension, but are associated with reduced cerebral flow and cause symptoms.

In provocative tests of physical, orthostatic and mental challenges, various symptoms are observed, especially after 12 to 24 hours of activity, known as "post-exertional malaise." Patients still have difficulty extracting oxygen during exertion, resulting in reduced anaerobic threshold.[67]

In the last decade, there has been an alarming increase in patients with other associated morbidities, such as chronic pain and functional impairment.[46-47] The same diagnostic criteria can be applied: chronic fatigue, chronic pain including headache, sleep disorders, mood disorders, post-exertional malaise, orthostatic and exercise intolerance and difficulty maintaining the usual functional capacity before the onset of symptoms.

Orthostatic intolerance is defined by the presence of dizziness, light head, visual turbidity and pre-syncope, which get worse in orthostatic position and are alleviated with horizontal posture.

Chronic diseases associated with chronic fatigue, as well as chronic fatigue alone, typically occur after a triggering event: Viral, bacterial or fungal infection, surgery, car accident, pregnancy, vaccination or after a prolonged period of physical or mental stress. Recently, infection with the new coronavirus (COVID-19) has been shown to affect several areas of the nervous system, with suspected cases of chronic fatigue being reported, causing concern about the possibility of a marked increase of this condition.[68-72]

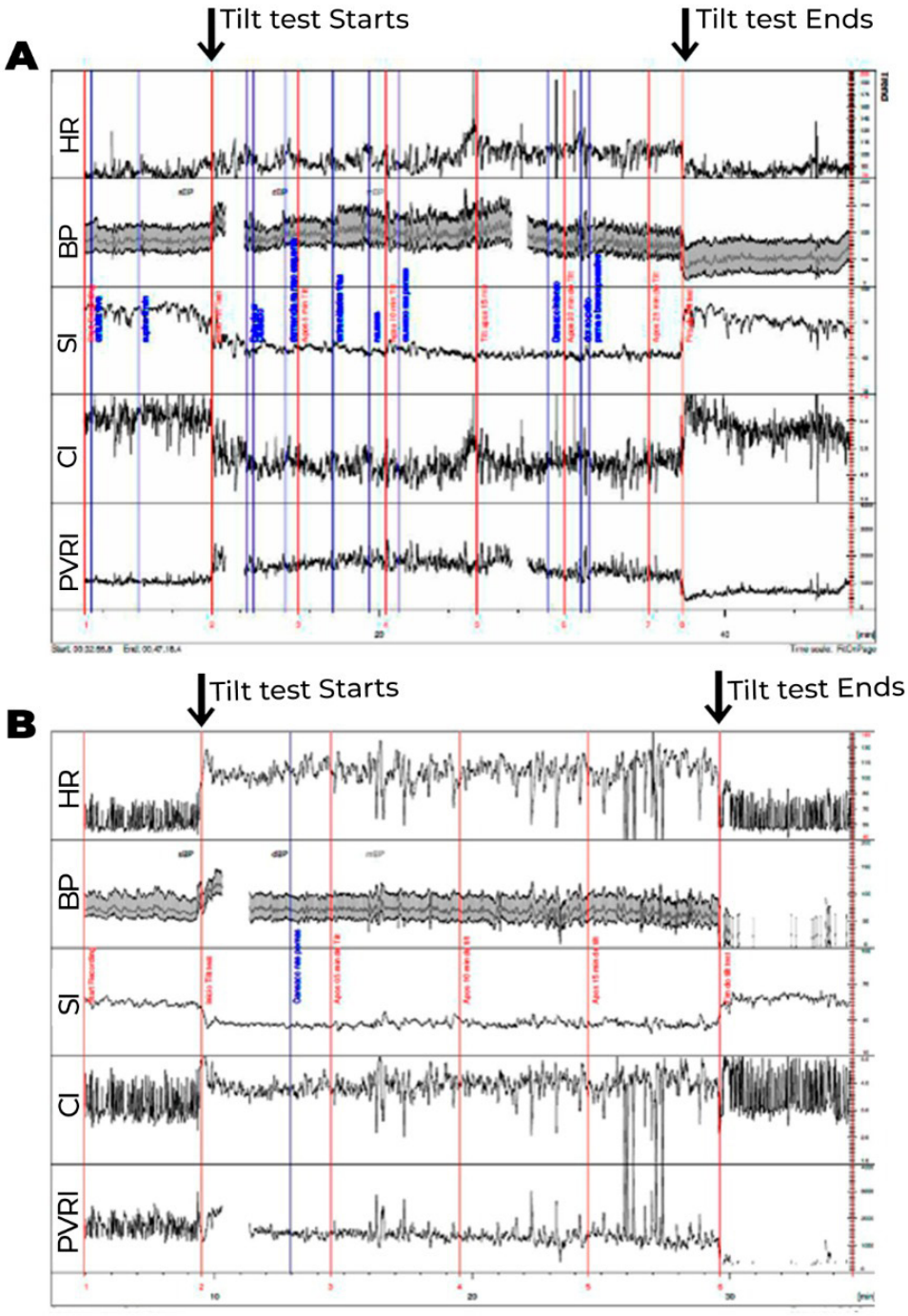


Figure 4 – *Tilt test with hemodynamic measurements, where systolic volume, cardiac output and peripheral vascular resistance (PVR) were corrected for body surface, resulting in systolic index (SI), cardiac index (CI) and PVR index (PVRI).*
4A. Patient with clinical diagnosis of chronic fatigue. Right after tilting, there is an exaggerated reduction in SI (>30%), initially compensated by the expected increase in PVRI and HR. After 15 minutes of tilting, there is a greater SI reduction associated with a PVRI reduction, instead of the greater compensatory increase expected of the PVRI. Therefore, the compensation to keep the BP stable occurs at the expense of a greater HR increase, which then presents excessive increase (>30 bpm), than in the supine position. This change occurs later (10 minutes after the beginning of the test), not fulfilling the criteria for POTS.
4B. Patient diagnosed with POTS. During the tilt test, an SI reduction is not compensated by a PVRI increase. PVRI decreases, rather than increases, in orthostatic position. Therefore, mean blood pressure (BP) remains stable due to an excessive increase in heart rate (HR) by >30 bpm, occurring in the first 10 minutes of tilting, associated with symptoms, thus fulfilling the POTS criteria.
The difference between the two conditions can be, in some cases, only time-related.

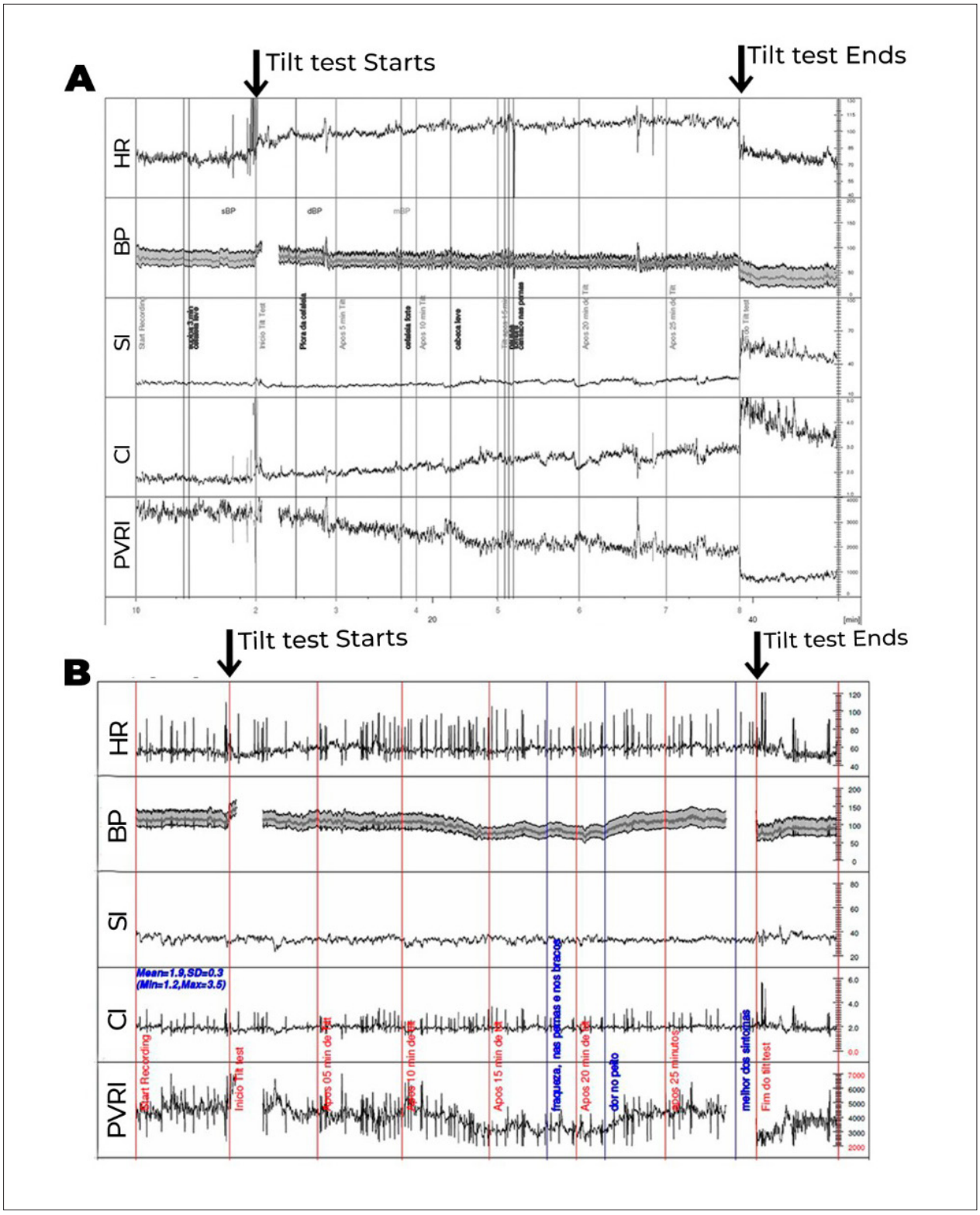


Figure 5 – *Tilt test with hemodynamic measures, where systolic volume, cardiac output and peripheral vascular resistance (PVR) were corrected for body surface, resulting in systolic index (SI), cardiac index (CI) and PVR index (PVRI). BP — blood pressure*
5A. Patient with orthostatic intolerance. There is no expected PVRI increase. Instead, it presents a progressive reduction compensated by a progressive increase in HR, until the end of tilting, with a slight reduction in BP. The symptoms occur in the presence of a deficit in PVR increase in an orthostatic position. 5B. Patient with late orthostatic hypotension. In this case, there no SI reduction and there is a progressive PVRI reduction during the tilt test. After 10 minutes of tilting, when there is a greater PVRI reduction, which is not accompanied by any additional HR increase, orthostatic hypotension is observed, with symptoms. After 20 minutes, spontaneous recovery of PVRI and BP occurs, with relief of symptoms.

In some cases, no precipitating factor is identified, but there may be family history of similar symptoms in first-degree relatives, suggesting a genetic component. Many patients develop anxiety and depression secondary to chronic diseases or as part of the pathophysiological abnormalities of the underlying disease. A significant number of patients have autoimmune and inflammatory markers.

Objective findings include: orthostatic intolerance to the tilt test, autonomic dysfunction and small fiber neuropathy (in autonomic function tests), hypovolemia and abnormality on functional magnetic resonance imaging (MRI) tests, single photon emission computed tomography (SPECT) or positron emission tomography (PET scan). Conventional MRI shows only non-specific findings.[69-71]

Despite recent discoveries, there is no highly sensitive and specific method for an accurate diagnosis yet, as there is no effective treatment.

As part of the treatment of chronic diseases associated with chronic fatigue, psychotherapy, cognitive behavioral therapy, and occupational therapy can improve the functional state and reduce the suffering of these patients. Medications are generally used for headache, neuropathic pain, muscle tension, gastrointestinal symptoms and sleep disorders. It is extremely useful to separate the different etiologies of chronic fatigue.

Mast cell activation syndrome can cause symptoms of chronic fatigue or POTS. In that case, antihistamines can be useful. In connective tissue diseases, anti-inflammatory drugs, immunomodulatory therapy such as chloroquine or intravenous immunoglobulin and corticosteroids can be used to control joint pain and fatigue.

Chronic Fatigue Syndrome — New criteria[8]

It has been recently recommended that chronic fatigue be renamed Systemic Exertion Intolerance Disease, with new diagnostic criteria:
1. Unexplained fatigue and consequent occupational disability for more than 6 months;
2. Post-exertional malaise;
3. Non-restorative sleep;
4. Cognitive impairment or orthostatic intolerance.

Postural Orthostatic Tachycardia Syndrome (POTS)

It is defined as an exaggerated chronotropic response to the change from horizontal posture to orthostasis, persistent and associated with symptoms of orthostatic intolerance (OI).[73,74] It is the most common cause of OI in the young population. It affects about 500,000 to 3,000,000 individuals in the United States alone, the majority of whom are females (4:1), aged 15 to 25 or at the beginning of their professional lives.[10,11,75] Sustained heart rate (HR) increase ≥30 bpm (≥40 bpm if <20 years old) or HR ≥120 bpm is observed in the first 10 minutes in an orthostatic position or during the tilt test, with no classical orthostatic hypotension associated. A slight decrease in blood pressure may occur.

Generally, one or more triggering factors are identified: acute stress such as pregnancy, surgery, previous infection, vaccine or traumatic event. Among the most common infections are: the mononucleosis virus (18.6%), respiratory (18%) and gastrointestinal (11.4%) viruses.[10,76,77]

In a preliminary evaluation of patients with suspected POTS, in addition to history taking and physical examination, vital signs must be taken in a supine and orthostatic position. Clinical history aims to investigate the potential causes of orthostatic tachycardia, including potential triggers. POTS symptoms are usually exacerbated by exercise, hot weather, dehydration and alcohol intake.

Electrocardiography and ambulatory ECG monitoring should be performed to rule out potential primary causes of tachycardia and echocardiography and exercise test to check for structural heart disease and heart rate response to exertion. Thyroid function tests, as well as blood count, should be part of the investigation routine, to rule out secondary causes of tachycardia.

The orthostatic tilt test can be useful to obtain hemodynamic parameters and tolerance to orthostatic position. Extended autonomic evaluation, with analysis of various hemodynamic parameters during the tilt test, is highly recommended in the investigation and differential etiological diagnosis of POTS.

Continuous and non-invasive BP and ECG monitoring systems, associated with bioimpedance measurements, allow to evaluate systolic volume, peripheral vascular resistance and cardiac output, making it possible to identify the type of hemodynamic disorder found in patients with POTS (Figures 4 and 5).

POTS is a heterogeneous syndrome resulting from different non-excluding pathophysiological mechanisms. It can be classified into five types, according to the prevailing pathophysiological mechanism: Neuropathic, hypovolemic, hyperadrenergic, secondary to noradrenaline abnormalities or activation of mast cells, and related to joint hypermobility (Ehlers-Danlos syndrome).[76-81]

In the neuropathic form, the main mechanism is impairment of peripheral vasoreactivity due to predominantly sympathetic denervation. In these cases, blood volume accumulates in the lower limbs in an orthostatic position and sympathetic system activation results in reflex tachycardia, which is not always compensatory. About 50% of these patients also have peripheral sudomotor denervation, suggesting post-ganglionic sympathetic denervation.

In the hypovolemic form, 70% of patients have hypovolemia due to excessive fluid retention in the lower compartment of the body. There is reduced tone, increased venous capacitance and reduced systolic volume during the tilt test. This central hypovolemia results in adrenergic activation by the baroreceptors and exacerbated compensatory reflex tachycardia.

Many patients in this group have reduced total blood volume, both in plasma and in blood cells.[78,79] Paradoxically, some of these patients have low levels of plasma renin and aldosterone activity and high levels of angiotensin II.[78]

In the Hyperadrenergic form, excessive adrenergic activation causes symptoms that include palpitations, sweating, tremors, anxiety and even hypertension triggered by physical activity or emotional stimulation. The primary hyperadrenergic form is characterized by high levels of plasma norepinephrine due to higher production (1000–2000 pg/ml), occurring in 5 to 10% of the cases.

The secondary form consists of a heterogeneous group divided into 3 main categories:

1. reduced clearance of synaptic norepinephrine (mutation of loss of function);

2. mast cell activation disorder — characterized by the presence of high urinary methylhistamine;

3. pharmacological blockade of norepinephrine transport by drugs that inhibit this transport, such as tricyclic antidepressants and other amphetamine-like drugs, the latter being the most frequently found type.

In the Ehlers-Danlos Syndrome, a connective tissue disease, with skin hyperelasticity and joint hypermotility, 70% of individuals have POTS and 18% of patients with POTS have diagnostic criteria for the Ehlers-Danlos syndrome, considered an underlying mechanism for the syndrome.[80]

In cases of patients with POTS with the mast cell activation syndrome, an autoimmune factor may be present. These patients have flushed skin and hypertension associated with orthostatic tachycardia. It is not yet clear whether sympathetic activation causes mast cell degranulation or whether mast cell activation causes vasodilation.[80,82]

In refractory patients, an extensive evaluation at a center specializing in autonomic tests should be considered. Valsalva's maneuvers with beat-to-beat BP measurement may show an exaggerated phase 4, revealing excessive sympathetic activity. Measurement of plasma epinephrine and norepinephrine in a supine and orthostatic position can be useful to identify hyperadrenergic cases, as well as analysis of 24-hour urinary sodium in cases of volume depletion.[6]

Anxiety and hypervigilance are often common in patients with POTS. However, HR increase is not due to an anxiety condition, but due to a physiological abnormality. Still, psychological assessment and follow-up can be useful in the clinical management of these patients.

Physical deconditioning is common to all forms of POTS. Multiple parameters associated with deconditioning are present in these patients: reduced cardiac area and mass (16%), reduced blood volume (20%) and reduced peak oxygen consumption (VO_2), compared to sedentary controls. Both bed rest and deconditioning reduce the baroreflex sensitivity to produce vasoconstriction.

In a study for international registration of POTS, progressive physical conditioning showed volume expansion and increased the cardiac area of patients, resulting in a significant improvement in symptoms. In this study, 71% of patients who completed the training program were free of POTS diagnosis. In a small group followed up for 6 to 12 months, the result was also maintained.[83]

The protocol consisted of 8 months of progressive training with aerobic exercise (3 sessions per week) associated with 2 weekly sessions of low-resistance muscle strengthening exercise, starting in the supine position and progressing to the orthostatic position. Compared to beta-blockers, exercise showed improved quality of life and normalized neurohumoral response, being considered class IIa of indication in international guidelines.[11,83,84]

There is no class I recommendation for the treatment of POTS. Non-pharmacological measures include increasing fluid intake to 2–3 liters/day and salt to 10–12 grams/day. Infusion of up to 2 liters of saline is recommended for acute decompensations (class IIb).[11]

If non-pharmacological measures are not effective, pharmacological treatment can be established according to the type of disorder identified (fFgures 4 and 5) or the modified algorithm proposed by Bryarly et al. (Figure 6).[74]

Chronic Fatigue Syndrome x Postural Orthostatic Tachycardia Syndrome (POTS)

Postural orthostatic tachycardia syndrome (SPOT) has been found in 29% of patients with chronic fatigue syndrome, while almost 50% of POTS patients have chronic fatigue syndrome.

Fludrocortisone may be useful in volume expansion, but its effect has not yet been tested in large clinical studies. Midodrine is an alpha-1 adrenergic agonist that increases the contraction of veins and arteries. This medication significantly reduces HR, but to a smaller extent than saline infusion. It has fast action and metabolization time and should be used 3 times a day, while the patient is active, avoiding potential nighttime hypertension.

Medications such as midodrine associated with a low dose of non-selective beta-blocker (propranolol), fludrocortisone and pyridostigmine are useful in the dysautonomic and hypovolemic forms of POTS. In the hyperadrenergic form, clonidine or alpha-methyldopa can be effective (class IIb).[11]

Sinus node modification by radiofrequency is not recommended and may be harmful, as it eliminates the compensatory mechanism of low cerebral output, which is sinus tachycardia, triggered by the baroreflex action.

Concomitant symptoms, such as headache and sleep disorders or gastrointestinal problems are often seen in POTS, and should be treated appropriately, as well as cognitive behavioral therapy should be considered.

Carotid Sinus Hypersensitivity and Cardioneuroablation

The prevalence of carotid sinus hypersensitivity (CSH) varies with age. It is extremely uncommon in individuals aged <50 and exponentially increases with age. In patients with syncope and age over 60, an abnormal carotid sinus response has been observed in up to 22.3%. Therefore, it is a common finding in elderly patients without syncope, especially if they have cardiovascular disease. For this reason, there is a consensus that for the diagnosis of carotid sinus hypersensitivity syndrome there is reproduction of clinical symptoms during carotid sinus massage and previous history of spontaneous syncope, suggestive of reflex origin.[12,85,86] Positive carotid sinus massage, but no history of syncope, only defines carotid sinus hypersensitivity and not the clinical syndrome (Table 6).

Carotid sinus massage is a class I indication in international guidelines for patients >40 years, with syncope of unknown origin, compatible with reflex mechanism (class I).[12] Massage is, however, controversial, as asymptomatic patients may present hemodynamic abnormalities with symptoms during maneuver.[87] However, if the syncope is of undetermined origin and the response to carotid sinus massage, in the cardioinhibitory form, reproduces the clinical symptom, there

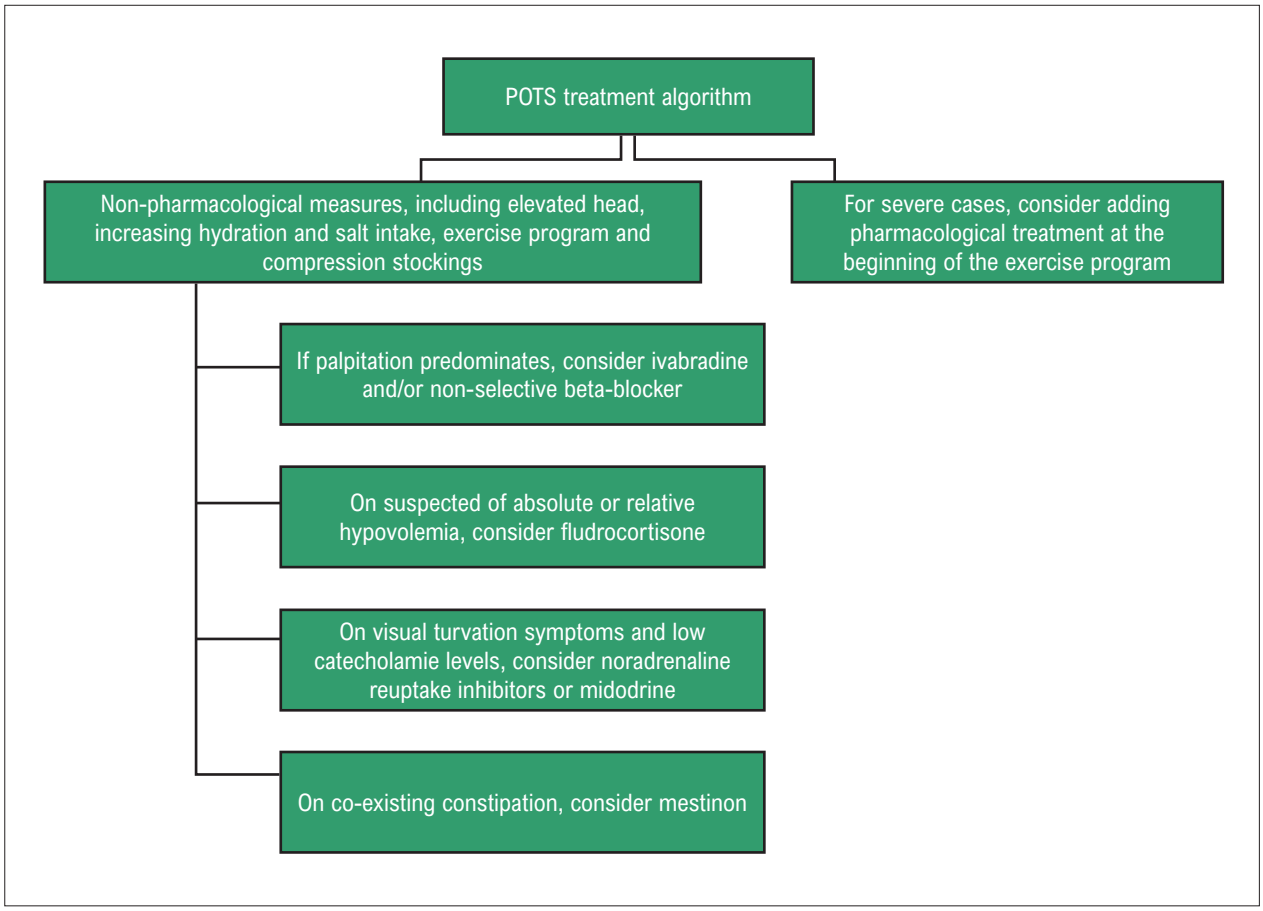


Figure 6 – *Treatment algorithm for patients with POTS. Source: adapted.*[74]

Table 6 – Definition of Carotid Sinus Hypersensitivity

DEFINITION
Reduced heart rate and/or blood pressure (BP) in response to carotid sinus massage:
1. Cardioinhibitory: pause ≥3 seconds (usually >6 seconds);
2. Vasodepressor: drop in BP ≥50 mmHg, with no significant bradycardia;
3. Mixed: pause ≥3 seconds associated with SBP drop ≥50 mmHg.

Source: Adapted[1]

is a presumptive cause of syncope, as the use of a pacemaker in this group of patients improved the symptoms of syncope in some studies.[11,88]

Perhaps the best way to confirm the cause of syncope in this context would be by long-term ECG monitoring (external or implantable looper). Although this technique (external or implantable looper) is more accurate to diagnose cases of carotid sinus hypersensitivity in the cardioinhibitory form, it would not be able to identify the vasodepressor forms of hypersensitivity.[89]

Carotid sinus massage should be preferably performed with continuous beat-to-beat BP and electrocardiogram monitoring. It is safer when performed at the tilt test facility. Maneuver should be performed with the patient's face rotated laterally, in a supine position and, if negative, it must be repeated in an orthostatic position, on each side, for a maximum of 10 seconds of compression, at the site of greatest carotid pulsation, at an angle formed by the mandible, the cricoid cartilage and the anterior margin of the sternocleidomastoid muscle. It should be avoided in patients with carotid murmur before adequate evaluation.

Although serious complications are rare (0.24%), the risk of transient ischemic attack must be considered, especially for patients who have previously experienced this event, as well as stroke or carotid artery stenosis >70%, as these are contraindications for the maneuver.[12]

The carotid sinus is a baroreceptor that responds to wall stretching, as with high BP.[65] In this situation, there is increased vagal tone and reduced sympathetic tone. Otherwise, on reduced BP and reduced vascular wall tension, there is a reduction in baroreceptor triggers, resulting in attenuation of vagal action. Baroreflex stimuli are sent from the carotid sinus to the solitary tract nucleus, where a large number of cardiovascular neurons are located.

Although the physiology of the carotid sinus baroreflex is reasonably well understood, the pathophysiology of CSH remains unclear.

Three main pathophysiological mechanisms have been considered:[90-94]

Atherosclerosis: theoretically, reduced vessel compliance could result in reduced afferent flow of the baroreflex impulse. However, it has been shown that the afferent portion of the carotid sinus reflex is intact in individuals with CSH.

Sternocleidomastoid muscle denervation:[92] with age, sternocleidomastoid muscle denervation (demonstrated by electromyography), thus reducing the information sent to the solitary tract nucleus, while the carotid sinus baroreceptors continue to send proper signals to the same nucleus, generating information imbalance. Thus, the head movement may result in afferent signals only from the carotid sinus, being interpreted by the solitary tract nucleus as an increase in BP, triggering an abrupt reduction in BP and HR.

Generalized autonomic dysfunction: high sympathetic activity has been recently demonstrated in individuals with CSH, symptomatic or asymptomatic, which suggests a generalized autonomic dysfunction.

The most common clinical manifestations of CSH are syncope, pre-syncope or dizziness during maneuvers with a change in head position. Loss of consciousness, as well as recovery, generally occur suddenly. Injuries resulting from falls are hence commonly observed.

Elderly patients may refer to episodes as recurrent falls, with no apparent cause. They may not report changes in head position during the fall.

Regarding treatment of the vasodepressor form of CSH, studies with midodrine[95] and fludrocortisone[96] showed improvement of syncope and presyncope symptoms compared to placebo. However, for patients with the cardioinhibitory form, definitive pacemaker implant has been the treatment of choice.

The decision to implant a pacemaker after a single episode of syncope will depend on the consequence and severity of the injury resulting from this episode. Some small observational randomized studies have shown improvement in clinical symptoms after implantation.[11,12,15]

However, randomized blinded studies comparing dual-chamber pacemakers versus dual-chamber pacemakers without active stimulation (off) did not show significant improvement in patients with unexplained falls.[88,90,97,98] Neither do large-scale randomized studies testing the use of pacemaker in cardioinhibitory form, raising questions about the recommendations of the current guidelines.[97] On the other hand, a meta-analysis of three studies showed 9% recurrence of syncope in patients with active stimulation, versus 38% in the control group (without a pacemaker).[99] This meta-analysis and other review studies are the basis of support for current recommendations for pacemaker implantation with Class IIa indication level, in American[15] and European[11,15] syncope guidelines.

Carotid sinus denervation by irradiation or endarterectomy has also been considered in the past as a treatment option.[100]

Regarding the prognosis, there has been no difference in mortality between patients with and without CSH compared to individuals of the same age.[87,101] However, the consequences of an injury resulting from a fall in an elderly patient cannot be adequately estimated. Therefore, patients must be informed that the risk of recurrent syncope should be reduced, but minor symptoms including pre-syncope may persist, even with therapies implemented.

Another very promising treatment strategy for reflex syncope resulting from exacerbated vagal activity is a technique known as cardioneuroablation, which consists of modifying vagal activity by catheter ablation, using radiofrequency energy.[102]

Pachon et al.[103] observed that when nerve fibers mix with myocardial cells, they produce changes in their conduction, from compact (uniform conduction with main frequency of 40 Hz, which occurs around very well-connected cells) to fibrillar conduction (conduction with fractional potentials with a frequency greater than 100 Hz). The authors used the fibrillar myocardial pattern (found mainly in the region of the sinus node and atrioventricular node) as a marker of neuromyocardial interface and target sites for cardioneuroablation and achieved clinical improvement of syncope episodes.[103]

Exciting results have been described in the literature with fibrillar myocardial ablation around the sinus node and atrioventricular node. During the ablation procedure, the disappearance of high-frequency potentials in these areas resulted in improved sinus and nodal function.[104]

Cardioneuroablation has been used to treat patients with carotid sinus hypersensitivity and can be an alternative to implanting a pacemaker, especially in young individuals, as these are more vulnerable to long-term complications.[105,106]

In summary, ablation of ganglionic plexuses can promote a significant reduction in vagal activity, in the sinus and atrioventricular nodes, and is effective in reducing symptoms in patients with severe neuromediated bradycardia. Due to the different techniques employed, randomized multicenter studies would be necessary to define the effectiveness, the best technique, safety and reproducibility of the method.[107]

Inappropriate Sinus Tachycardia (IST)

The first case of inappropriate sinus tachycardia (IST) was described in the literature in 1939 by Codvelle and Boucher.[108] A prevalence of 1.2% is currently estimated in the general population.[11] It is considered a chronic condition, but little is known about its evolution and mortality. Its mechanism is poorly understood,[109-113] including increased sinus node automaticity, beta-adrenergic hypersensitivity, reduced parasympathetic activity and impaired neurohormonal modulation.

The onset of symptoms is usually associated with a stressful event, such as a divorce of parents of teenagers, separation or another major family event. The symptoms usually found are:

palpitations, dizziness, and syncope. Abdominal discomfort, sweating, headache, visual turbidity, fatigue, anxiety, exercise intolerance, myalgia and chest pain may also occur.

Clinical history and physical examination must be performed to identify the potential causes for tachycardia, such as: hyperthyroidism; medicines; use of hidden substances; psychological triggers; panic attacks, and to rule out POTS, considering that both conditions share the same symptoms (Table 7).

Patients should be investigated for hypovolemia, which is observed in some cases. However, it is necessary to rule out structural heart disease for the diagnosis of IST. In the natural history of patients with IST, in general, there is no worsening of ventricular function due to tachycardia.[109] However, there are rare descriptions of isolated cases of tachycardiomyopathy, challenging the assumption that IST is always a benign condition.[111,113,114]

Stress testing can be useful in documenting exaggerated tachycardia in response to exercise. Cardiovascular autonomic tests, including HR response to Valsalva maneuver, deep breathing and orthostatic position, as well as HR variability and baroreflex sensitivity, have not shown clinical usefulness and, therefore, should not be routinely employed.[11]

Inappropriate Sinus Tachycardia (IST)

It is characterized when the resting heart rate is greater than 100 bpm and the average HR is greater than 90 bpm on 24-h Holter in adolescents and young adults. It occurs more commonly in women, without a reasonable cause. It is associated with various severe and often debilitating symptoms, especially palpitations, dizziness and syncope.

People with IST usually experience a significant loss of quality of life. There are no placebo-controlled prospective clinical studies for the therapeutic interventions used in the treatment, and some symptoms may persist despite HR control.

There is some evidence that ivabradine, at a dose of 5 to 7.5 mg, twice a day, can improve quality of life. [115,116,117] In addition, it appears that ivabradine may have benefits when associated with beta-blockers (metoprolol).[118]

Beta-blockers alone are not useful and can cause side effects. Other treatments have been proposed, such as: drugs such as fludrocortisone; clonidine; erythropoietin; non-pharmacological measures, such as elastic compression stockings; physical exercises and, rarely, radiofrequency ablation, which may pose risks of sinus node injury, requiring the implantation of a cardiac pacemaker.[119] Patients with IST usually require special attention and lifestyle changes.

Note

Part II of this article, which describes clinical and cardiovascular symptoms, methods of investigation and treatment, will continue in the next issues of the journal.

Author contributions

Conception and design of the research: Rocha EA; Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Rocha EA, Mehta N, Távora-Mehta MZP, Roncari CF, Cidrão AAL, Elias Neto J; Statistical analysis: Elias Neto J

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.

Sources of Funding

There was no external funding source for this study.

Study Association

This study is not associated with any thesis or dissertation.

Table 7 – Causes that must be ruled out before diagnosing inappropriate sinus tachycardia

Medical Conditions	Physiological Conditions	Drugs/Substances
Hyperthyroidism	Physical exercise	Caffeine
Cushing disease	Emotional stress	Alcohol
Pheochromocytoma	Pain	Tobacco
Anemia	Fever	Catecholamines
Infections	Pregnancy	Vasodilators
Dehydration	Volume depletion	Substances with atropine
Cardiomyopathy		Theophylline
Panic attack		Illicit drugs
Pericarditis		Decongestants
Mitral or aortic regurgitation		Sympathomimetics
Myocardial infarction		Thyroid-stimulating hormones
Orthostatic hypotension		

Source: author and adapted.[10,110]

References

1. Spallone V, Ziegler D, Freeman R, Bernardi L, Frontoni S, Pop-Busui R, et al. Cardiovascular autonomic neuropathy in diabetes: clinical impact, assessment, diagnosis, and management. Diabetes Metab Res Rev. 2011 Oct;27(7):639–53.
2. Spallone V. Update on the impact, diagnosis and management of cardiovascular autonomic neuropathy in diabetes: what is defined, what is new, and what is unmet. Diabetes Metab J. 2019 Feb;43(1):3–30.
3. Gibbons CH, Schmidt P, Biaggioni I, Frazier-Mills C, Freeman R, Isaacson S, et al. The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension. J Neurol. 2017;264(8):1567–82.
4. Jordan J, Fanciulli A, Tank J, Calandra-Buonaura G, Cheshire WP, Cortelli P, et al. Management of supine hypertension in patients with neurogenic orthostatic hypotension: scientific statement of the American Autonomic Society, European Federation of Autonomic Societies, and the European Society of Hypertension. J Hypertens. 2019 Aug;37(8):1541–6.
5. Vinik AI, Camacho PM, Davidson JA, Handelsman Y, Lando HM, Leddy AL, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Position Statement on Testing for Autonomic and Somatic Nerve Dysfunction. Endocr Pract. 2017 Dec;23(12):1472–8.
6. Spallone V, Bellavere F, Scionti L, Maule S, Quadri R, Bax G, et al. Recommendations for the use of cardiovascular tests in diagnosing diabetic autonomic neuropathy. Nutr Metab Cardiovasc Dis. 2011;21(1):69–78.
7. Freeman R, Abuzinadah AR, Gibbons C, Jones P, Miglis MG, Sinn DI. Orthostatic hypotension. J Am Coll Cardiol. 2018;72(11):1294–309.
8. Institute of Medicine, Board on the Health of Select Populations, Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Beyond Myalgic Encephalomyelitis/Chronic Fatigue Syndrome: Redefining an Illness. Washington (DC): National Academies Press; 2015.
9. Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins JG, Komaroff A. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. Ann Intern Med.1994;121(12):953-9.
10. Sheldon RS, Grubb 2nd BP, Olshansky B, Shen WK, Calkins H, Brignole M, et al. 2015 heart rhythm society expert consensus statement on the diagnosis and treatment of postural tachycardia syndrome, inappropriate sinus tachycardia, and vasovagal syncope. Heart Rhythm. 2015 Jun;12(6):e41–63.
11. Brignole M, Moya A, Lange FJ , Deharo JC, Elliott PM, Fanciulli A, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J. 2018;39(21):1883–948.
12. Brignole M, Moya A, Lange FJ, Deharo JC, Elliott PM, Fanciulli A, et al. Practical Instructions for the 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J. 2018 Jun 1;39(21):e43–80.
13. Gondim FAA, Barreira AA, Claudino R, Cruz MW, Cunha FMB, Freitas MRG, et al. Definition and diagnosis of small fiber neuropathy: consensus from the Peripheral Neuropathy Scientific Department of the Brazilian Academy of Neurology. Arq Neuro-Psiquiatr. 2018;76(3):200–8.
14. Tesfaye S, Boulton AJM, Dyck PJ, Freeman R, Horowitz M, Kempler P, et al. Diabetic neuropathies: update on definitions, diagnostic criteria, estimation of severity, and treatments. Diabetes Care. 2010;33(10):2285–93.
15. Shen WK, Sheldon RS, Benditt DG, Cohen MI, Forman DE, Goldberger ZD, et al. 2017 ACC/AHA/HRS Guideline for the Evaluation and Management of Patients With Syncope: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. J Am Coll Cardiol.2017;Aug 1;70(5):620-63.
16. Bernardi L, Spallone V, Stevens M, Hilsted J, Frontoni S, Pop-Busui R, et al. Methods of investigation for cardiac autonomic dysfunction in human research studies. Diabetes Metab Res Rev. 2011;27(7):654–64.
17. Shibao C, Lipsitz LA, Biaggioni I. ASH position paper: evaluation and treatment of orthostatic hypotension. J Clin Hypertens. 2013;15(3):147–53.
18. Ricci F, De Caterina R, Fedorowski A. Orthostatic Hypotension: Epidemiology, Prognosis, and Treatment. J Am Coll Cardiol. 2015 Aug 18;66(7):848–60.
19. Freeman R, Wieling W, Axelrod FB, Benditt DG, Benarroch E, Biaggioni I, et al. Consensus statement on the definition of orthostatic hypotension, neurally mediated syncope and the postural tachycardia syndrome. Clin Auton Res. 2011;21(2):69-72.
20. Langley JN. The autonomic nervous system. Cambridge: W. Heffer & Sons; 1921.
21. Hasan W. Autonomic cardiac innervation. Organogenesis. 2013;9(3):176–93.
22. Jose AD, Collison D. The normal range and determinants of the intrinsic heart rate in man. Cardiovasc Res. 1970;4(2):160–7.
23. Opthof T. The normal range and determinants of the intrinsic heart rate in man. Cardiovascular Research. 2000;45(1):177–84.
24. Schreihofer AM, Guyenet PG. The baroreflex and beyond: control of sympathetic vasomotor tone by GABAergic neurons in the ventrolateral medulla. Clin Exp Pharmacol Physiol. 2002;29(5):514–21.
25. Smit AA, Halliwill JR, Low PA, Wieling W. Pathophysiological basis of orthostatic hypotension in autonomic failure. J Physiol. 1999 Aug 15;519(Pt 1):1–10.
26. Ponte CMM, Fernandes VO, Gurgel MHC, Vasconcelos ITGF, Karbage LBAS, Liberato CBR, et al. Early commitment of cardiovascular autonomic modulation in Brazilian patients with congenital generalized lipodystrophy. BMC Cardiovasc Disord. 2018 Jan 12;18(1):6.
27. Rolim LCSP, Sá JR, Chacra AR, Dib SA. Diabetic cardiovascular autonomic neuropathy: risk factors, clinical impact and early diagnosis. Arq Bras Cardiol. 2008 Apr;90(4):e24–31.
28. Pop-Busui R, Evans GW, Gerstein HC, Fonseca V, Fleg JL, Hoogwerf BJ, et al. Effects of cardiac autonomic dysfunction on mortality risk in the action to control cardiovascular risk in diabetes (ACCORD) trial. Diabetes Care. 2010;33(7):1578–84.
29. Maser RE, Mitchell BD, Vinik AI, Freeman R. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes: a meta-analysis. Diabetes Care. 2003 Jun;26(6):1895–901.
30. Vinik AI, Casellini C, Parson HK, Colberg SR, Nevoret ML. Cardiac autonomic neuropathy in diabetes: a predictor of cardiometabolic events. Front Neurosci. 2018 Aug 27;12:591.
31. Low PA, Vernino S, Suarez G. Autonomic dysfunction in peripheral nerve disease. Muscle Nerve. 2003 Jun;27(6):646–61.
32. Shy GM, Drager GA. A neurological syndrome associated with orthostatic hypotension: a clinical-pathologic study. Arch Neurol. 1960 May;2:511–27.
33. Committee on the Diagnostic Criteria for Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Beyond myalgic encephalomyelitis/chronic fatigue syndrome: redefining an illness. Washington (DC): National Academies Press; 2015. V. 46.
34. Vernino S, Low PA, Fealey RD, Stewart JD, Farrugia G, Lennon VA. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. N Engl J Med. 2000 Sep 21;343(12):847–55.
35. Low PA. Laboratory evaluation of autonomic function. In: Clinical Autonomie Disorders, 2nd ed. Philadelphia: Lippincott-Raven; 1997.
36. Andrade C. A peculiar form of peripheral neuropathy; familiar atypical generalized amyloidosis with special involvement of the peripheral nerves. Brain. 1952 Sep;75(3):408–27.

37. Corino de Andrade. BMJ. 2005;331:163.

38. Bittencourt PL, Couto CA, Clemente C, Farias AQ, Palacios SA, Mies S, et al. Phenotypic expression of familial amyloid polyneuropathy in Brazil. Eur J Neurol. 2005;12(4):289–93.

39. Kittleson MM, Maurer MS, Ambardekar AV, Bullock-Palmer RP, Chang PP, Eisen HJ, et al. Cardiac amyloidosis: evolving diagnosis and management: a scientific statement from the American Heart Association. Circulation. 2020;142(1):e7-22.

40. Berk J, Damy T, Drachman B, Elliott P, Gottlieb S, Grogan M,et all. Efficacy of tafamidis in transthyretin amyloid cardiomyopathy in the ATTR-ACT trial. Heart Lung. 2019;48(5):470.

41. Ruzieh M, Dasa O, Pacenta A, Karabin B, Grubb B. Droxidopa in the treatment of postural orthostatic tachycardia syndrome. Am J Ther. 2017;24(2):e157–61.

42. Loavenbruck A, Sandroni P. Neurogenic orthostatic hypotension: roles of norepinephrine deficiency in its causes, its treatment, and future research directions. Curr Med Res Opin. 2015;31(11):2095–104.

43. Ruzieh M, Batizy L, Dasa O, Oostra C, Grubb B. The role of autoantibodies in the syndromes of orthostatic intolerance: a systematic review. Scand Cardiovasc J. 2017 Oct;51(5):243–7.

44. Amorim DS, Neto JAM. Functional alterations of the autonomic nervous system in Chagas' heart disease. Sao Paulo Med J. 1995;113(2):772–84.

45. Junqueira Jr LF. Insights into the clinical and functional significance of cardiac autonomic dysfunction in Chagas disease. Rev Soc Bras Med Trop. 2012 Mar;45(2):243–52.

46. Dávila DF, Inglessis G, Dávila CAM. Chagas' heart disease and the autonomic nervous system. Int J Cardiol. 1998;66:123–7.

47. Chagas C, Villela E. Cardiac form of American Trypanosomiasis. Mem Inst Oswaldo Cruz. 1922;14(1):5–61.

48. Goin JC, Borda E, Leiros CP, Storino R, Sterin-Borda L. Identification of antibodies with muscarinic cholinergic activity in human Chagas' disease: pathological implications. J Auton Nerv Syst. 1994 Apr;47(1-2):45–52.

49. Ribeiro ALP, Moraes RS, Ribeiro JP, Ferlin EL, Torres RM, Oliveira E, et al. Parasympathetic dysautonomia precedes left ventricular systolic dysfunction in Chagas disease. Am Heart J. 2001;141(2):260–5.

50. Punukollu G, Gowda RM, Khan IA, Navarro VS, Vasavada BC. Clinical aspects of the Chagas' heart disease. Int J Cardiol. 2007;115(3):279–83.

51. Ribeiro ALP, Campos MS, Baptista LMG, Sousa MR. The Valsalva maneuver in Chagas disease patients without cardiopathy. Clin Auton Res. 2010;20(2):79–83.

52. Marino VSP, Dumont SM, Mota LG, Braga DS, Freitas SS, Moreira MCV. Sympathetic dysautonomia in heart failure by 123I-MIBG: comparison between Chagasic, non-Chagasic and heart transplant patients. Arq Bras Cardiol. 2018 Aug;111(2):182–90.

53. Nunes MCP, Dones W, Morillo CA, Encina JJ, Ribeiro AL, Council on Chagas Disease of the Interamerican Society of Cardiology. Chagas disease: an overview of clinical and epidemiological aspects. J Am Coll Cardiol. 2013 Aug 27;62(9):767–76.

54. Sterin-Borda L, Borda E. Role of neurotransmitter autoantibodies in the pathogenesis of chagasic peripheral dysautonomia. Ann N Y Acad Sci. 2000;917:273–80.

55. Velten APC, Benseñor I, Souza JB, Mill JG. Factors associated with orthostatic hypotension in adults: the ELSA-Brasil study. Cad Saúde Pública. 2019;35(8):e00123718.

56. Marin-Neto JA. Cardiac dysautonomia and pathogenesis of Chagas' heart disease. Int J Cardiol. 1998 Sep 30;66(2):129–31.

57. Elias Neto J, Kuniyoshi RR, Silva MA, Merçon E. Taquicardia ventricular polimórfica durante teste de inclinação na doença de Chagas. J Card Arrhythm. 2017;30(2):51–4.

58. Fanciulli A, Jordan J, Biaggioni I, Calandra-Buonaura G, Cheshire WP, Cortelli P, et al. Consensus statement on the definition of neurogenic supine hypertension in cardiovascular autonomic failure by the American Autonomic Society (AAS) and the European Federation of Autonomic Societies (EFAS) : Endorsed by the European Academy of Neurology (EAN) and the European Society of Hypertension (ESH). Clin Auton Res. 2018 Aug;28(4):355–62.

59. Távora-Mehta MZP, Mehta N, Magajevski A, Oliveira L, Maluf DLS, Concato L, et al. Reduced systolic volume: main pathophysiological mechanism in patients with orthostatic intolerance? Arq Bras Cardiol. 2016;107(4):354-64.

60. Low PA. Neurogenic orthostatic hypotension: pathophysiology and diagnosis. Am J Manag Care.2015;21(13 Suppl):s248–57.

61. Zilliox L, Peltier AC, Wren PA, Anderson A, Smith AG, Singleton JR, et al. Assessing autonomic dysfunction in early diabetic neuropathy: the survey of autonomic symptoms. Neurology. 2011;76(12):1099–105.

62. Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. Mayo Clin Proc. 1993 Aug;68(8):748–52.

63. Lewis I, Pairman J, Spickett G, Newton JL. Clinical characteristics of a novel subgroup of chronic fatigue syndrome patients with postural orthostatic tachycardia syndrome. J Intern Med. 2013;273(5): 501–10.

64. Carruthers BM, Sande MI, De Meirleir KL, Klimas NG, Broderick G, Mitchell T, et al. Myalgic encephalomyelitis: International Consensus Criteria. J Intern Med. 2011;270(4):327–38.

65. Mueller C, Lin JC, Sheriff S, Maudsley AA, Younger JW. Evidence of widespread metabolite abnormalities in Myalgic encephalomyelitis/chronic fatigue syndrome: assessment with whole-brain magnetic resonance spectroscopy. Brain Imaging Behav. 2020;14(2):562–72.

66. Campen CLMC, Rowe PC, Visser FC. Blood volume status in ME/CFS correlates with the presence or absence of orthostatic symptoms: preliminary results. Front Pediatr. 2018 Nov 15;6:352.

67. Stevens S, Snell C, Stevens J, Keller B, VanNess JM. cardiopulmonary exercise test methodology for assessing exertion intolerance in myalgic encephalomyelitis/chronic fatigue syndrome. Front Pediatr. 2018 Sep 4;6:242.

68. Solve M.E. What does COVID-19 portend for ME/CFS; 2020. [acesso 30 jan 2021]. Disponível em: https://solvecfs.org/covid/.

69. Blitshteyn S, Chopra P. Chronic fatigue syndrome: from chronic fatigue to more specific syndromes. Eur Neurol. 2018;80(1-2):73–7.

70. Sotzny F, Blanco J, Capelli E, Castro-Marrero J, Steiner S, Murovska M, et al. Myalgic encephalomyelitis/chronic fatigue syndrome – evidence for an autoimmune disease. Autoimmun Rev. 2018;17(6):601–9.

71. Komaroff A, Cho TA. Role of infection and neurologic dysfunction in chronic fatigue syndrome. Semin Neurol. 2011;31(3):325–37.

72. Komaroff AL. Advances in understanding the pathophysiology of chronic fatigue syndrome. JAMA. 2019;322(6):499-500.73.

73. Bryarly M, Phillips LT, Fu Q, Vernino S, Levine BD. Postural orthostatic tachycardia syndrome: JACC Focus Seminar. J Am Coll Cardiol. 2019 Mar 19;73(10):1207–28.

74. Thieben MJ, Sandroni P, Sletten DM, Benrud-Larson LM, Fealey RD, Vernino S, et al. Postural orthostatic tachycardia syndrome: the Mayo clinic experience . Mayo Clin Proc. 2007;82(3):308–13.

75. Zadourian A, Doherty TA, Swiatkiewicz I, Taub PR. Postural orthostatic tachycardia syndrome: prevalence, pathophysiology, and management. Drugs. 2018 Jul;78(10):983–94.

76. Boris JR, Bernadzikowski T. Demographics of a large paediatric Postural Orthostatic Tachycardia Syndrome Program. Cardiol Young. 2018;28(5):668–74.

77. Levin KH, Chauvel P.. Clinical neurophysiology: diseases and disorders. Amsterdam: Elsevier BV; 2019. (Handbook of clinical neurology 3rd series; vol. 161).

78. Raj SR, Biaggioni I, Yamhure PC, Black BK, Paranjape SY, Byrne DW, et al. Renin-aldosterone paradox and perturbed blood volume regulation underlying postural tachycardia syndrome. Circulation. 2005;111(13):1574–82.

79. Fu Q, VanGundy TB, Melyn Galbreath M, Shibata S, Jain M, Hastings JL, et al. Cardiac origins of the postural orthostatic tachycardia syndrome. J Am Coll Cardiol. 2010;55(25):2858–68.

80. Wallman D, Weinberg J, Hohler AD. Ehlers-Danlos Syndrome and Postural Tachycardia Syndrome: a relationship study. J Neurol Sci. 2014 May 15;340(1-2):99–102.

81. Garland EM, Celedonio JE, Raj SR. Postural Tachycardia Syndrome: beyond orthostatic intolerance. Curr Neurol Neurosci Rep. 2015 Sep;15(9):60.

82. Shibao C, Arzubiaga C, Jackson Roberts L, Raj S, Black B, Harris P, et al. Hyperadrenergic Postural Tachycardia Syndrome in mast cell activation disorders. Hypertension. 2005;45(3):385–90.

83. George SA, Bivens TB, Howden EJ, Saleem Y, Melyn Galbreath M, Hendrickson D, et al. The international POTS registry: evaluating the efficacy of an exercise training intervention in a community setting. Heart Rhythm. 2016;13(4):943–50.

84. Fu Q, Vangundy TB, Shibata S, Auchus RJ, Williams GH, Levine BD. Exercise training versus propranolol in the treatment of the postural orthostatic tachycardia syndrome. Hypertension. 2011 Aug;58(2):167–75.

85. Krediet CTP, Parry SW, Jardine DL, Benditt DG, Brignole M, Wieling W. The history of diagnosing carotid sinus hypersensitivity: why are the current criteria too sensitive? Europace. 2011;13(1):14–22.

86. Kerr SRJ, Pearce MS, Brayne C, Davis RJ, Kenny RA. Carotid sinus hypersensitivity in asymptomatic older persons. Arch Intern Med. 2006;166(5):515-20.

87. Wu TC, Hachul DT, Darrieux FCC, Scanavacca MI. Carotid sinus massage in syncope evaluation: a nonspecific and dubious diagnostic method. Arq Bras Cardiol. 2018;111(1):84-91.

88. Parry SW, Steen N, Bexton RS, Tynan M, Kenny RA. Pacing in elderly recurrent fallers with carotid sinus hypersensitivity: a randomised, double-blind, placebo controlled crossover trial. Heart. 2009;95:405–9.

89. Elias Neto J, Vasconcelos DM,Merçon ES, Silva MA< Kuniyoshi R. Ablação do splexos gangliônicos parassimpáticos cardíacos no tratamento da síncope neuromediada cardioinibitória em paciente com monitor de evento implantável. Arquivos Brasileiros de Cardiologia.2018;111(5):S1.

90. Amin V, Pavri BB. Carotid sinus syndrome. Cardiol Rev. 2015;23(3):130–4.

91. Kenny RA, Lyon CC, Ingram AM, Bayliss J, Lightman SL, Sutton R. Enhanced vagal activity and normal arginine vasopressin response in carotid sinus syndrome: implications for a central abnormality in carotid sinus hypersensitivity. Cardiovasc Res. 1987;21(7):545–50.

92. Blanc J-J, L'Heveder G, Mansourati J, Tea SH, Guillo P, Mabin D. Assessment of a newly recognized association. Carotid sinus hypersensitivity and denervation of sternocleidomastoid muscles. Circulation. 1997;95(11):2548–51.

93. Tan MP, Kenny RAM, Chadwick TJ, Kerr SRJ, Parry SW. Carotid sinus hypersensitivity: disease state or clinical sign of ageing? Insights from a controlled study of autonomic function in symptomatic and asymptomatic subjects. Europace. 2010 Nov;12(11):1630–6.

94. Kumar NP, Thomas A, Mudd P, Morris RO, Masud T. The usefulness of carotid sinus massage in different patient groups. Age Ageing. 2003;32(6):666–9.

95. Moore A, Watts M, Sheehy T, Hartnett A, Clinch D, Lyons D. Treatment of vasodepressor carotid sinus syndrome with midodrine: a randomized, controlled pilot study. J Am Geriatr Soc. 2005;53(1):114–8.

96. Costa D, McIntosh S, Kenny RA. Benefits of fludrocortisone in the treatment of symptomatic vasodepressor carotid sinus syndrome. Br Heart J. 1993;69(4):308–10.

97. Parry SW. Should we ever pace for carotid sinus syndrome? Front Cardiovasc Med. 2020;7(44):1-11.

98. Ryan DJ, Nick S, Colette SM, Roseanne K. Carotid sinus syndrome, should we pace? A multicentre, randomised control trial (Safepace 2).Heart. 2010;96(5):347-51.

99. Brignole M, Menozi C. The natural history of carotid sinus syncope and the effect of cardiac pacing . Europace.2011;13:462-4.

100. Trout 3rd HH, Brown LL, Thompson JE. Carotid sinus syndrome. Ann Surg. 1979;189(5): 575–80.

101. Brignole M, Oddone D, Cogorno S, Menozzi C, Gianfranchi L, Bertulla A. Long-term outcome in symptomatic carotid sinus hypersensitivity. Am Heart J. 1992;123(3):687–92.

102. Pachon JC, Pachon EI, Pachon JC, Lobo TJ, Pachon MZ, Vargas RNA, et al. "Cardioneuroablation" – new treatment for neurocardiogenic syncope, functional AV block and sinus dysfunction using catheter RF-ablation. Europace. 2005;7(1):1–13.

103. Pachon-M JC. Neurocardiogenic syncope: Pacemaker or cardioneuroablation? Heart Rhythm. 2020;17(5 PtA):829–30.

104. Lu CS, Guo CJ, Fang DP, Hao P, He D-F, Xu AG. Initial experience with ablation of the innervation surrounding sinus and atrioventricular nodes to treat paroxysmal bradyarrhythmia. Chin Med J. 2020 Jan 20;133(2):134–40.

105. Palamà Z, De Ruvo E, Grieco D, Borrelli A, Sciarra L, Calò L. Carotid sinus hypersensitivity syncope: is there a possible alternative approach to pacemaker implantation in young patients? Postepy Kardiol Interwencyjnej. 2017;13(2):184–5.

106. Pachon M JC, Pachon M EI, Lobo TJ, Pachon M JC, Pachon MZC, Vargas RNA, et al. Syncopal high-degree AV block treated with catheter RF ablation without pacemaker implantation. Pacing Clin Electrophysiol. 2006;29(3):318–22.

107. Scanavacca M, Hachul D. Ganglionated plexi ablation to treat patients with refractory neurally mediated syncope and severe vagal-induced bradycardia. Arq Bras Cardiol. 2019;112(6):709-12.

108. Codvelle MM, Boucher H. Tachycardie sinusale permanente à haute fréquence sans troubles fonctionnels. Bull Mem Soc Med Hop Paris. 1939;54:1849–52.

109. Olshansky B, Sullivan RM. Inappropriate sinus tachycardia. J Am Coll Cardiol. 2013;61(8):793–801.

110. Chiale PA, Garro HA, Schmidberg J, Sánchez RA, Acunzo RS, Lago M, et al. Inappropriate sinus tachycardia may be related to an immunologic disorder involving cardiac β andrenergic receptors. Heart Rhythm. 2006;3(10):1182–6.

111. Peyrol M, Lévy S. Clinical presentation of inappropriate sinus tachycardia and differential diagnosis. J Interv Card Electrophysiol. 2016 Jun;46(1):33–41.

112. Winum PF, Cayla G, Rubini M, Beck L, Messner-Pellenc P. A case of cardiomyopathy induced by inappropriate sinus tachycardia and cured by ivabradine .Pacing Clin Electrophysiol. 2009;32(7):942–4.

113. Morillo CA, Klein GJ, Thakur RK, Li H, Zardini M, Yee R. Mechanism of "inappropriate" sinus tachycardia. Role of sympathovagal balance. Circulation. 1994;90(2):873–7.

114. Sag S, Coskun H, Baran I, Güllülü S, Aydinlar A. Inappropriate sinus tachycardia-induced cardiomyopathy during pregnancy and successful treatment with ivabradine. Anatol J Cardiol. 2016;16(3):212-13.

115. Shabtaie SA, Witt CM, Asirvatham SJ. Natural history and clinical outcomes of inappropriate sinus tachycardia. J Cardiovasc Electrophysiol. 2020 Jan;31(1):137–43.

116. Cappato R, Castelvecchio S, Ricci C, Bianco E, Vitali-Serdoz L, Gnecchi-Ruscone T, et al. Clinical efficacy of ivabradine in patients with inappropriate sinus tachycardia: a prospective, randomized, placebo-controlled, double-blind, crossover evaluation. J Am Coll Cardiol. 2012;60(15):1323–9.

117. Ptaszynski P, Kaczmarek K, Cygankiewicz I, Klingenheben T, Urbanek I, Wranicz JK. Ivabradine in patients with synptomatic inapprioprate sinus tachycardia:long-term observational study. J Am Coll Cardiol. 2017;69(11):306.

118. Ptaszynski P, Kaczmarek K, Ruta J, Klingenheben T, Cygankiewicz I, Wranicz JK. Ivabradine in combination with metoprolol succinate in the treatment of inappropriate sinus tachycardia. J Cardiovasc Pharmacol Ther. 2013;18(4):338–44.

119. Marrouche NF, Beheiry S, Tomassoni G, Cole C, Bash D, Dresing T, et al. Three-dimensional nonfluoroscopic mapping and ablation of inappropriate sinus tachycardia. Procedural strategies and long-term outcome. J Am Coll Cardiol. 2002;39(6):1046–54.

Double Outlet Right Ventricle with Unrelated Ventricular Septal Defect and Pulmonary Stenosis, in Natural Evolution, in a 36-Year-Old Woman

Edmar Atik[1]

Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo,[1] *São Paulo, SP – Brazil*

Introduction

The congenital defect, characterized by the exit of both large arteries from the right ventricle (RV), completely or even when overlapping more than 50% of one of the arteries over the interventricular septum, presents variable relationships between these arteries and the ventricular septal defect (VSD), as well as association with other anatomical and functional variables.[1]

In the most common associated defect, the isolated VSD, in a subaortic position or in that unrelated to the large arteries, the functional condition is expressed with a predominance of volume overload of the heart as a whole, increased by pressure overload, causing early heart failure.

In associated defects such as coarctation of the aorta, mitral stenosis and even when the VSD is restrictive, there is an increase in the pulmonary congestive condition. Association with atrioventricular septal defect, abnormalities of cardiac position and atrial isomerism, also reinforce this picture.

In the association of VSD with infundibular and valvar pulmonary stenosis, another type of complication of cardiovascular dynamics appears, responsible for the appearance of varied hypoxia. Cyanosis is progressively more intense depending on the accentuation of pulmonary stenosis, a picture similar to that presented in the tetralogy of Fallot. The same occurs in patients submitted to previous pulmonary banding.

In subpulmonary VSD (Taussig-Bing type), accentuation of pulmonary arterial flow with volume overload of the left cavities is responsible for congestive heart failure, expressed by pulmonary venocapillary plethora. Hypoxemia is generally mild in this condition, and is accentuated when interatrial communication is restrictive. Hypoxia is more intense in association with pulmonary stenosis. Early clinical exteriorization in the first days of life is similar to that found in the transposition of the great arteries with VSD.

Keywords

Double Outlet Right Ventricle; Heart Defects, Congenital/surgery; Heart Septal Defects Ventricular; Diagnostic, Imaging; Pulmonary Valve Stenosis; Adult.

Mailing Address: Edmar Atik •
Rua Dona Adma Jafet, 74 cj 73. Postal Code 01308-050, São Paulo, SP - Brazil
E-mail: edmar.atik@incor.usp.br
Manuscript received September 01, 2020, revised manuscript October 14, 2020, accepted eito em 14/10/2020

DOI: https://doi.org/10.36660/abc.20200971

In general, clinical variations depend on the intensity of the obstructive defects, the size of intercavitary communications and associated defects, which together increase cardiovascular dynamics.

Sometimes, in the association of pulmonary stenosis and VSD, there may be a balance of flows, systemic and pulmonary, in such a way that the patient progresses to adulthood without manifestations, but with possible future complications, given the pressure overload imposed on the RV.

In this tuning fork, the clinical expectant conduct adopted in patients who are progressing favorably at earlier ages, as children or young people, becomes debatable.

This would be the main reason for the discussion and presentation of the following case.

Case Description

Clinical data: A 36-year-old patient developed palpitations for 8 years due to ventricular and supraventricular extrasystoles, even with the use of propafenone. She reports good tolerance to usual physical exertion and uses hypothyroidism levothyroxine. Infectious endocarditis was treated at 17 years of age. The family rejected the idea of surgical intervention in the first decade of life, considering that at that time the patient was in good general condition and without symptoms.

Physical examination: Good general condition, eupneic, acyanotic, normal pulses in the four limbs. Weight: 55 Kg, Height: 165 cm, BP: 100x65 mmHg, CF: 79 bpm, O_2 Sat.= 96%.

Precordium: Apical impulse not palpable, without systolic impulses on the left external border. Accentuated heart sounds, moderate systolic murmur on the upper left external edge, without thrill, 3/6 + intensity. No palpable liver and clear lungs.

Complementary Exams

Electrocardiogram: Sinus rhythm, with "rs" morphology in V1, with the "r" wave being thickened and notched (AQRS= +60º). There was diastolic right ventricular overload with negative T wave in V1, and the presence of left potentials with qRs complex in V6, with high R waves from V4 to V6. There were no changes in ventricular repolarization (AT = + 60º), and P wave was normal (AP = + 50º) (Figure 1).

Chest radiography: Mild to moderate increase in the cardiac area at the expense of the long, rounded left ventricular arch (CTI = 0.57). Increased pulmonary vascular network being more prominent in the hilum on the right, with a convex medium arch. Normal aortic arch (Figure 1).

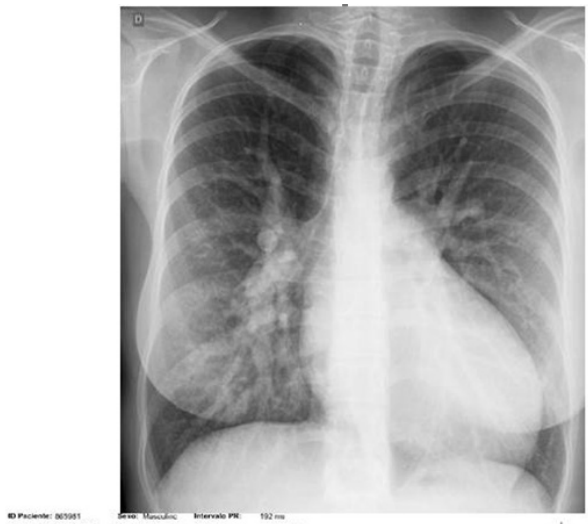


Figure 1 – *Chest X-ray shows a slight to moderate increase in the cardiac area at the expense of the elongated and rounded left ventricular arch (CTI = 0.57). Increased pulmonary vascular network being well protruding from the hilum on the right with a convex arch. Electrocardiogram highlights the diastolic overload of both ventricles.*

Echocardiogram: Concordant atrioventricular connection and double outlet of both arteries from the RV, being the anterior aorta at right side. The inferior vena cava was dilated with 21 mm, with spontaneous contrast. The inlet VSD with extension to the outlet route was wide and unrelated, measuring 26 mm, with bidirectional flow, preferably from left to right and without restriction, and without an interventricular pressure gradient. The atria were enlarged, especially on the left (LA = 51 mm). Hypertrophic and dilated RV with preserved systolic function. In the outflow tract there was infundibular stenosis and also at the pulmonary valve level, with a systolic gradient of 85 mm Hg. The left ventricle (LV) was hypertrophic and dilated (67 mm) with normal function. The diameter of the aorta was 35 mm and the pulmonary arteries confluent, the right with 28 mm and the left with 24 mm. The tricuspid valve was 30 mm and the mitral valve was 25 mm (Figure 2).

Angiotomography: The diagnosis was confirmed with measurements similar to those of the echocardiogram, with the left atrium and the two ventricular cavities enlarged. The biventricular function was normal. The pulmonary artery was posterior to the left and the aorta to the right and anterior (Figure 2).

Holter: Ventricular extrasystoles (3% of total beats), without supraventricular or ventricular tachycardias. Heart rate ranged from 51 to 116 bpm, with an average of 76 bpm.

Ergospirometry: Maximum oxygen consumption adjusted for body weight of 22.3 ml/kg/min. Blood pressure at rest was 100x60 mmHg at 75 bpm and at maximum effort was 130x60 mmHg at 155 bpm.

Clinical diagnosis: Double outlet RV with the anterior and right aorta, with great unrelated VSD at the inlet portion, and infundibulo-valve pulmonary stenosis, in natural evolution in adulthood.

Clinical Characteristics

A) Clinical Reasoning: There were clinical elements of diagnostic guidance for congenital heart disease, with arterial malposition due to accentuated heart sounds and pulmonary stenosis in the presence of systolic ejection murmur in the pulmonary area, with irradiation to the left external border. The right ventricular diastolic overload on the electrocardiogram with clear LV potentials express the presence of two well-formed ventricles and hence the presence of associated VSD. The obstructive pulmonary defect counterbalances that of VSD, in such a way that the patient

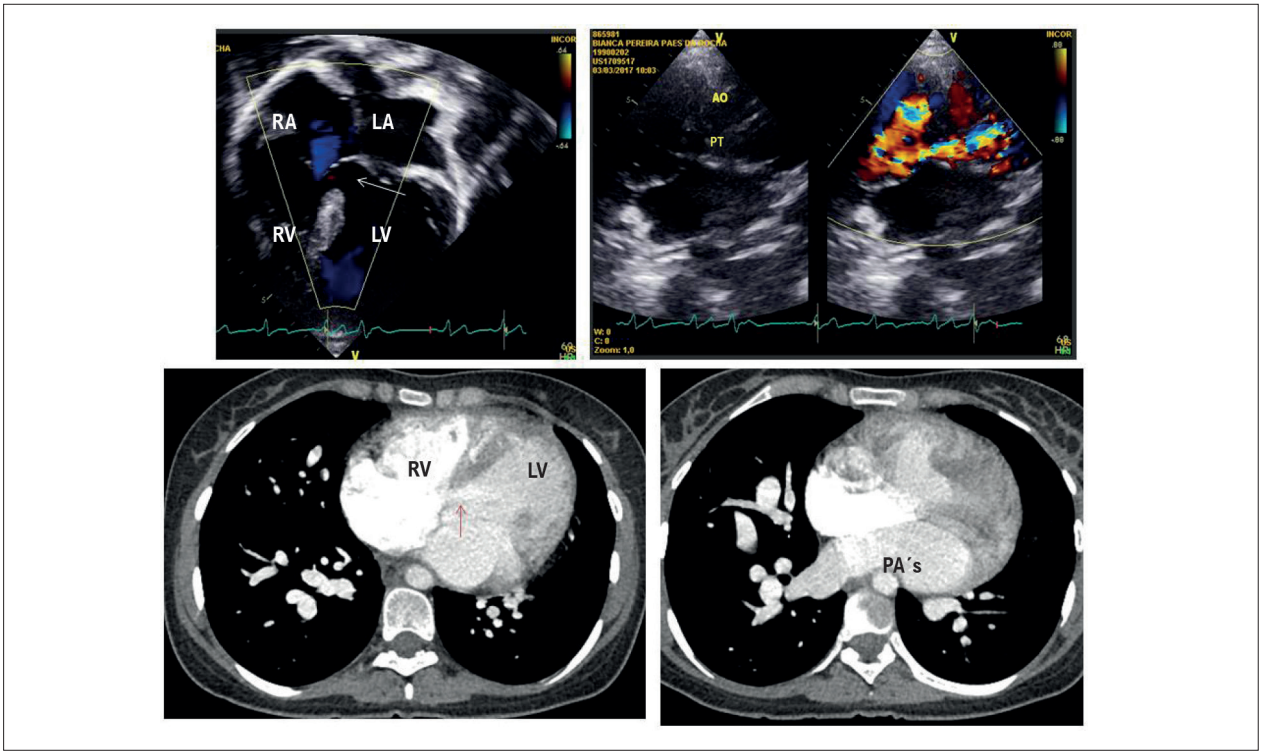


Figure 2 – *Echocardiogram shows, in a 4-chamber view, the large interventricular communication (arrow) of the entry route and in subcostal view, the two large vessels emerging from the right ventricle with the aorta to the right of the pulmonary. Pulmonary obstruction begins in the infundibular region. Cardiac tomography highlights ventricular cavities and dilated pulmonary arteries in addition to interventricular communication (arrow). RA: right atrium; LA: left atrium; RV: right ventricle; LV: left ventricle; PT: pulmonary trunk; PA´s: pulmonary arteries.*

remained without cyanosis, with preferential flow from left to right and without symptoms. The elaborated clinical diagnosis was well established by echocardiography and tomography.

B) Differential diagnosis: This general picture can be found in other defects that are similar in this dynamics of VSD and pulmonary stenosis, such as in the transposition of the great arteries and in the double entry way of the LV or RV, in the atresia of the atrioventricular valves and in the corrected transposition of the great arteries. Other elements of the usual complementary exams differentiate them.

Conduct: In view of the balance of pulmonary and systemic flows over time, with no signs of hypoxemia and / or heart failure and in the presence of good physical tolerance, the continuity of the expectant clinical conduct was considered.

Discussion

The natural evolution of this patient until adulthood highlights unfavorable elements, although she has been shown to be in good clinical and hemodynamic conditions. They are acquired characters that interfere with the evolution over a longer period of time. They correspond to the increase in cardiac cavities, due to accentuated pulmonary flow in the previous period of time, and to the progression of pulmonary stenosis, with cardiac hypertrophy and dilation. Despite the maintenance of good ventricular function, the patient is subject to the appearance of other adverse factors such as accentuated arrhythmias, diastolic heart failure, the appearance of progressive hypoxemia, of infective endocarditis, causes of the probable evolutionary clinical lack of control.[1]

On the other hand, little can be offered at this point, from the surgical point of view, as the presumed technique as the most appropriate would be Fontan's functional, contraindicated by the current absence of hypoxia. The corrective technique would be very difficult due to the presence of unrelated VSD and the anterior aorta.[2] Hence, in similar cases in childhood, one wonders whether it would be more convenient to try to correct it, in that age group, even with a considerable surgical risk.

When recalling surgical techniques, subaortic VSD involves tunneling with bovine pericardium, dacron or goretex of blood flow from the LV to the aorta. This defect can be amplified when restricting the flow, on the anterior face of the same, thus avoiding the infero-dorsal conduction beam. In the presence of pulmonary stenosis, the correction is similar to that performed in the tetralogy of Fallot with resection of the infundibular muscle, through the atrial route or by right ventriculotomy, in addition to the pulmonary valvotomy with enlargement of the pulmonary ring and subsequent placement of the monocuspid. A valve graft between the RV and the pulmonary trunk may be necessary, when it is located posteriorly or when the coronary artery is positioned in the ventricular outflow tract, close to the pulmonary ring. In the

absence of correction, when the RV is hypoplastic, it guides the total cavopulmonary operation as described in the single functional or anatomical ventricle. In turn, in subpulmonary VSD, the LV is directed to the pulmonary trunk. Thus, arterial and coronary artery exchange follow the same tactics recommended according to Jatene's correction.

Postoperative evolution generally follows the preferred and necessary technique depending on the anatomical type. More intense problems are seen in the postoperative management when placing connection tubes between the RV and the pulmonary trunk, in view of obstruction and/or valve failure in the evolution.

Arrhythmias can complicate the evolution when in association with atrial isomerism, ventricular dysfunction and in postoperative residual defects.

Due to this clinical presentation, due to the specific association of pulmonary stenosis and unrelated VSD, the functional condition becomes more dependent on the repercussion of the obstructive lesion. Pulmonary stenosis can decrease the repercussion of VSD and there is a counterbalance such that the pulmonary and systemic flows are equivalent. Therefore, the patient can remain without volume overloads and symptoms and progress properly until adulthood, without manifestation. However, systolic overload of the RV due to pulmonary stenosis and the slight repercussion of left ventricular volume can, in the long run, cause evolutionary problems such as heart failure, arrhythmias, which obscure the results, and put life at risk.[1]

In the presence of unrelated VSD as in the case on display, the technique devised by Barbero-Marcial[3] directs the LV to the aorta with tunneling with patches from the VSD to the aortic valve, and with relief of pulmonary stenosis, applied with relative success in survival rate of 86.5% after 10 years.[4,5] Another technique, such as directing VSD to the pulmonary artery and subsequent arterial exchange is also feasible.

It is concluded, therefore, that the most appropriate management in these patients, even with balance of flows, systemic and pulmonary, is that of corrective intervention at earlier ages, even if the patient is in good clinical condition.[5-7]

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Atik E.

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.

References

1. Atik E, Moreira VM. Dupla via de saída de ventrículo direito. In:Atik E, Moreira VM: Imagens e Correlações em Cardiologia Pediátrica. São Paulo: Editora Roca Ltda; 2011. P.137-45.
2. Pang KJ, Meng H, Hu SS, Wang H, Hsi D, Hua ZD, et al.. chocardiographic Classification and Surgical Approaches to Double-Outlet Right Ventricle for Great Arteries Arising Almost Exclusively from the Right Ventricle. Tex Heart Inst J. 2017 Aug 1;44(4):245-51.
3. Barbero-Marcial M, Tanamati C, Atik E, Ebaid M. Intraventricular repair of double-outlet right ventricle with non-committed ventricular septal defect: advantages of multiple patches. J Thorac Cardiovasc Surg. 1999; 118(6):1056– 67.
4. Villemain O, Belli E, Ladouceur M, Houyel L, Jalal Z, Lambert V, et al. Impact of anatomic characteristics and initial biventricular surgical strategy on outcomes in various forms of double-outlet right ventricle. J Thorac Cardiovasc Surg. 2016 Sep;152(3):698-706.
5. Kahr PC, Alonso-Gonzalez R, Kempny AC, Konstantinos U, Lorna SH, et al. Long-term Natural History and Postoperative Outcome of Double-Chambered Right Ventricle-Experience From Two Tertiary Adult Congenital Heart Centres and Review of the Literature Int J Cardiol. 2014 1;174(3):662-8.
6. Ting Lu , Jia Li, Jianguo Hu, Can Huang, Ling Tan, Qin Wu, et al. Biventricular Repair of Double-Outlet Right Ventricle With Noncommitted Ventricular Septal Defect Using Intraventricular Conduit J Thorac Cardiovasc Surg 2020;159(6):2397-403.
7. Lacour-Gayet F. Biventricular Repair of Double Outlet Right Ventricle With Noncommitted Ventricular Septal Defect Semin Thorac Cardiovasc Surg Pediatr Card Surg Annu. 2002; 5:163-72.

Porcine Valve Bioprosthesis: a Legacy from Mario Vrandecic

Erika Correa Vrandecic,[1] Ektor Correa Vrandecic,[1] Bayard Gontijo-Filho,[1] Rossana Dall'Orto Elias,[1] Braulio Roberto Gonçalves Marinho Couto,[1] Marcus Vinicius Bolivar Malachias[1,2]

Biocor Institute,[1] Nova Lima, MG - Brazil

Faculdade de Ciências Médicas de Minas Gerais,[2] Belo Horizonte, MG - Brazil

Heart valve disease currently occupies the spotlight in cardiovascular medicine due to recent advances in imaging techniques and emerging therapeutic possibilities, attracting the attention of physicians, researchers, device manufacturers, and investors.[1] Brazil has a prominent international role in the history and technological development of prosthetic heart valves used to treat this disease.

The first worldwide implantation of a commercially available porcine valve bioprosthesis occurred in October 1968.[2] About half a century later, in September 2019, passes on the physician and scientist Mario Vrandecic, creator of the only heart valve bioprosthesis made from porcine tissue produced in Brazil and approved by the United States (US) Food and Drug Administration (FDA), globally used for decades in the treatment of heart valve disease.

In this article, we highlight the history of the creator and the evidence of effectiveness and safety of the Biocor valve bioprosthesis, known today as St. Jude Medical Biocor (St. Jude Medical, Inc., St Paul, MN).[3-16]

Mario Vrandecic, of Croatian ancestry and a native of Bolivia, studied medicine at the School of Medicine at *Universidade Federal de Minas Gerais* (FM/UFMG). He specialized in general and cardiovascular surgery in the US, where he served in the US army as a surgeon, including during the Vietnam War. He returned permanently to Brazil in 1976 and started working as a professor at FM/UFMG and as a cardiovascular surgeon at *Santa Casa de Belo Horizonte*, among other hospitals.

Having conducted research on biological tissues during his residency in the US, Vrandecic created in 1981 the Biocor Indústria, where he developed a heart valve bioprosthesis made of porcine tissue, among other patents. Initially used in Brazil, Central America, and Asia, the bioprosthesis soon obtained CE Marking, and was used in Europe and, with later FDA approval, also in the US. He received honors from several scientific societies and national and international entities in the area of innovation. In 1997, Biocor Indústria was sold to the US company St. Jude Medical, which was acquired by Abbott Laboratories later in 2016.

After almost 40 years of clinical use, evidence of short-, medium-, and long-term follow-up has demonstrated the effectiveness, durability, and safety of the valve bioprosthesis in national and international series (Table 1).[3-16] In one of the most prolonged follow-up periods, Mykén and Bech-Hansen evaluated 1712 patients who received the Biocor porcine bioprosthesis at Sahlgrenska University Hospital (Gothenburg, Sweden), demonstrating rates of freedom from valve-related death at 20 years of 84.3 ± 6.9% and 88.0% ± 4.0% for aortic and mitral valve replacement, respectively[16] (Table 1).

Mario Vrandecic also founded, in 1985, the Biocor Institute, located in Nova Lima, metropolitan region of Belo Horizonte, MG. Initially dedicated to cardiovascular diseases, the hospital soon evolved into an important high-complexity medical center. The hospital has been responsible for specialization and work of many generations of cardiologists, cardiac surgeons, physicians of various specialties, and other health care professionals, in addition to being a reference in quality assistance to the population of the state, with important national and international certifications. Mario Vrandecic's management was based on ethics, generation of trust, qualification of individuals, and continuing education. His legacy symbolizes an example of humanism and dedication to medicine, a landmark of innovation in cardiovascular science, and a testament to the country's biotechnological potential.

Keywords

Heart Valve Diseases/surgery; Heart Valve Prosthesis Implantation; Bioprosthesis/trends; Mario Vranderic.

Mailing Addess: Marcus Vinicius Bolivar Malachias •
Biocor Institute – Rua Mario Vrandecic, 250. Postal Code 34006-059, Bairro Vila da Serra, Nova Lima, MG - Brazil
E-mail: mbolivar@cardiol.br

Manuscript received October 15, 2020, revised manuscript November 18, 2020, accepted November 18, 2020

DOI: https://doi.org/10.36660/abc.20201110

Author contributions

Conception and design of the research, Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Vrandecic EC, Vrandecic EC, Gontijo-Filho B, Elias RD, Couto BRGM, Malachias MVB; Acquisition of data: Vrandecic EC, Vrandecic EC, Gontijo-Filho B; Statistical analysis Vrandecic EC, Couto BRGM, Malachias MVB; Writing of the manuscript: Vrandecic EC, Couto BRGM, Malachias MVB.

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.

Sources of Funding

There was no external funding source for this study.

Study Association

This study is not associated with any thesis or dissertation.

Table 1 – Clinical outcomes observed in patients who received aortic and mitral valve replacement with the Biocor porcine bioprosthesis*

Author/ Reference	Follow-up period	Bioprosthesis position	Sample size (n)	Outcome	Observed outcome
Vrandecic [3,4]	March 1981 - March 1988 (48 [1 to 84] months)	Aortic + Mitral	1713	In-hospital mortality	6.1%
				Survival at 7 years	97.1%
		Aortic	385	Late complications	13.2%
				Freedom from valve dysfunction at 7 years	96.9%
		Mitral	716	Late complications	14.2%
				Survival at 7 years	95.2%
Gontijo-Filho[5]	May 1990 - March 1992 (9 [1 to 22] months)	Aortic	81	In-hospital mortality	4.9%
Gontijo-Filho[6]	June 1990 -January 1993	Aortic "stentless" in aortic annulus abnormalities	16	In-hospital mortality	6.3%
Vrandecic[7]	March 1992 -March 1993 (6 [1 to 12] months)	Mitral	38	In-hospital mortality	0%
				Valve reoperation	3.8%
Vrandecic[8]	May 1990 -December 1993	Aortic "stentless"	120	In-hospital mortality	5%
				Valve reoperation	4%
Vrandecic[9]	(14 [1 to 26] months)	Mitral "stentless"	85	In-hospital mortality	0%
				Valve reoperation	6%
Vrandecic[10]	March 1992 -December 1995 (26 [3 to 45] months)	Mitral "stentless"	108	In-hospital mortality	6.5%
				Valve reoperation	12.5%
Vrandecic[11]	March 1992 -August 1996 (29 [2 to 54] months)	Mitral “stentless"	120	In-hospital mortality	6.5%
				Valve reoperation	14.3%
Vrandecic[12]	January 1990 -June 1999 (54 [3 to 114] months)	Aortic "stentless" vs. "stented"	407	8-year survival	71.8 ± 0.7% (“stentless”) vs. 62.9 ± 13.4% (“stented”)
Kirali[13]	January 1985 -June 1999 (10 [1 to 15] years)	Mitral	158	30-day mortality	4.4%
				Valve reoperation	14%
				5-year cumulative survival	83.7±3%
				13-year cumulative survival	77.8±3.4%
				Freedom from structural valve deterioration at 5 years	95.5±1.8%
				Freedom from structural valve deterioration at 13 years	64.8±5.3%
				Freedom from structural valve deterioration-related reoperation at 5 years	98.4±1.1%
				Freedom from structural valve deterioration-related reoperation at 10 years	89.2±2.9%
				Freedom from structural valve deterioration-related reoperation at 14 years	76.8±7.9%

Continuation

Pomerantzeff[14]	March 1983 - December 2000	Mitral	546	In-hospital mortality	9.5%
				15-year survival	45±15.8%
				Freedom from structural valve deterioration-related reoperation at 15 years	33.9 ± 10.4%
Eichinger[15]	January 1985 -December 2006 (8 [1 to 21] years)	Aortic	455	30-day mortality	5.3%
				5-year survival	74.7% ± 2.0%
				10-year survival	44.9% ± 2.4%,
				15-year survival	20.9% ± 2.5%
				20-year survival	9.4% ± 2.8%.
				Freedom from nonstructural valve dysfunction at 5 years	97.5 % ± 0.8%
				Freedom from nonstructural valve dysfunction at 10 years	93.1% ± 1.7%
				Freedom from nonstructural valve dysfunction at 15 years	88.4% ± 3.5%
				Freedom from nonstructural valve dysfunction at 20 years	70.3% ± 10.9%
				Freedom from reoperation due to structural valve deterioration at 5 years	95.9% ± 1%
				Freedom from reoperation due to structural valve deterioration at 10 years	91.9% ± 1.6%
				Freedom from reoperation due to structural valve deterioration at 15 years	90.6% ± 2.1%
				Freedom from reoperation due to structural valve deterioration at 20 years	86.5% ± 4.5%
Mykén[16]	January 1983 -January 2003 (mean 6 years)	Aortic	1518	In-hospital mortality	5.1%
				Incidence of reoperation	0.9%/ patient-year
				Freedom from valve-related death at 20 years	84.3 ± 6.9%
				Freedom from reoperation due to structural valve deterioration at 20 years	61.1% ± 8.5%
		Mitral	194	In-hospital mortality	12.9%
				Incidence of reoperation	0.9%/ patient-year
				Freedom from valve-related death at 20 years	88.0% ± 4.0%
				Freedom from reoperation due to structural valve deterioration at 20 years	79.3% ± 6.0%

** Data from 14 publications evaluating short-, medium-, and long-term outcomes with the Biocor Porcine Bioprosthesis, published between 1988 and 2008.3-16*

References

1. Binder RK, Dweck M, Prendergast B. The year in cardiology: valvular heart disease. Eur Heart J. 2020; 41(8): 912-20.
2. Bortolotti U, Milano AD, Valente M, Thiene G. The Stented Porcine Bioprosthesis: a 50-year journey through hopes and realities. Ann Thorac Surg. 2019; 108(1):304-8.
3. Vrandecic MO, Filho BG, Silva JAP,Fantini FA, Barbosa IT, São Jose MC, et al. Clinical results with the Biocor porcine bioprosthesis. J Cardiovasc Surg (Torino). 1991; 32(6): 807-13.
4. Vrandecic MO, Filho BG, Silva JAP,Radegran KI, Silva JAP< Fantini FA, et al. Estudo multicêntrico dos resultados das trocas valvares com o uso da bioprótese Biocor no Estado de Minas Gerais. Rev Bras Cir Cardiovasc. 1988; 3(3): 159-68.
5. Gontijo Filho B, Vrandecic MO, Morea M, Morea M, Nova bioprótese aórtica sem suporte: resultados clínicos. Rev Bras Cir Cardiovasc. 1992; 7(3): 208-14.
6. Gontijo Filho B, Vrandecic MO, Fantini FA,Barbosa JT, Avelar SS,et al. Implante de bioprótese aórtica "stentless" em pacientes com alterações do anel aórtico. Rev Bras Cir Cardiovasc. 1993; 8(2): 118-24.
7. Vrandecic MO, Filho BG, Fantini FA , Barbosa JT, Silva JAP, Barbosa JT, Gutierrez C, et al. Transplante de valva mitral heteróloga: nova alternativa cirúrgica: estudo clínico inicial. Rev Bras Cir Cardiovasc. 1993; 8(2): 83-90.
8. Vrandecic MO, Filho BG, Fantini FA, Oliveira OC, Martins Jr IC, Bioprótese aórtica porcina "stentless": acompanhamento clínico a médio prazo. Rev Bras Cir Cardiovasc. 1994; 9(1): 60-3.
9. Vrandecic MOP, Fantini FA, Gontijo BF,Oliveira OC, Martins Jr JC. Surgical technique of implanting the stentless porcine mitral valve. Ann Thorac Surg. 1995; 60 (2 Suppl): S439–S442.
10. Vrandecic MO, Filho BG, Fantini FA, Martins MH, Avelar SS, Vandrecic E. Valva mitral heteróloga sem suporte: resultados clínicos a médio prazo. Rev Bras Cir Cardiovasc. 1996; 11(3): 148-54.
11. Vrandecic MO, Gontijo B, Fantini FA,Martins I, Oliveira MH, Avelar SS, et al. Porcine mitral stentless valve mid-term clinical results. Eur J Cardiothorac Surg. 1997; 12(1): 56-62.
12. Vrandecic M, Fantini FA, Filho BG, Filho BG, Oliveira OC, Costa Jr IM, et al. Retrospective clinical analysis of stented vs stentless porcine aortic bioprostheses. Eur J Cardiothorac Surg. 2000; 18: 46-53.
13. Kirali K, Güler M, Tuncer A, Daglar B, Ipek G, Isik O, et al. Fifteen-year clinical experience with the biocor porcine bioprostheses in the mitral position. Ann Thorac Surg. 2001; 71(3): 811-5.
14. Pomerantzeff PM, Brandão CM, Albuquerque JM, Stolf NA, Grinberg M, Oliveira AS. Long-term follow up of the Biocor porcine bioprosthesis in the mitral position. J Heart Valve Dis. 2006; 15(6): 763-7.
15. Eichinger WB, Hettich IM, Ruzicka DJ, Holper K, Schricker C, Bleiziffer S, et al. Twenty-year experience with the St. Jude medical Biocor bioprosthesis in the aortic position. Ann Thorac Surg. 2008; 86(4):1204-10.
16. Mykén PS, Bech-Hansen O. A 20-year experience of 1712 patients with the Biocor porcine bioprosthesis. J Thorac Cardiovasc Surg. 2009; 137(1): 76-81.

HIV-Infected Naïve Patients Exhibit Endothelial Dysfunction Concomitant with Decreased Natural Antibodies Against Defined Apolipoprotein B Autoantigens

Henrique Andrade R. Fonseca,[1,2] Magnus Gidlund,[2] Viviane Rodrigues Sant'Anna,[1,2] Esteferson Rodrigues Fernandes,[1,2] Francisco A. H. Fonseca,[1] Maria Cristina Izar[1]

Universidade Federal de São Paulo Escola Paulista de Medicina,[1] São Paulo, SP - Brazil

Universidade de Sao Paulo,[2] São Paulo, SP - Brazil

Backgorund: Traditional and HIV-defined risk factors may be associated with an increase in cardiovascular events. Recent studies have suggested that the humoral immune response to modified LDL may be associated with the process of atherosclerosis.

Objectives: To evaluate the presence of anti-oxLDL and apolipoprotein B-derived peptides in the blood, and their association with the endothelial function in HIV-infection.

Methods: This study consecutively included subjects matched for age, gender, and demographic data in two groups: (1) HIV-infected and naïve for antiviral therapy and (2) uninfected individuals. Subclinical atherosclerosis was assessed by intimal-media thickness, using ultrasonography of the carotid arteries. Endothelial function was determined by flow-mediated dilatation (FMD) of the brachial artery by ultrasonography. Autoantibodies (IgM, IgG) anti-oxidized low-density lipoprotein (oxLDL), anti-apolipoprotein B-peptide fragments (ApoB-D and 0033G-Cys peptides), and cytokine levels were evaluated by ELISA.

Results: This study's results showed no difference in subclinical atherosclerosis between groups; however, HIV-infected subjects showed a lower FMD, when compared to non-infected subjects. Therefore, HIV-infected subjects showed higher levels of inflammatory cytokines, titers of IgG anti-oxLDL, and IgG anti-ApoB-D. In contrast, titers of IgM anti-ApoB-D were lower in HIV-infected individuals and associated with reduced endothelial functions.

Conclusions: This study's results show that HIV infection, in naïve subjects, is associated with endothelial dysfunction and a decline of natural antibodies to apo-B antigens.

Keywords: HIV Infection; Atherosclerosis; Endothelium Vascular; Apolipoproteunes B, Carotid Arteries/ultrasonography.

Cardiovascular disease is more prevalent in HIV-infected, as compared to non-infected, individuals.[1] Endothelial dysfunction (ED) is the initiating event in plaque formation, associated with sub-endothelial space inflammation caused by low density lipoprotein (LDL) oxidation.[2,3] Detection of LDL oxidation can be a marker of atherosclerosis processes and/or progression.[4]

To overcome some of the obstacles related to the lack of more restricted epitopes than those expressed in an artificial oxidation process (copper, iron, and others) to generate oxidized LDL (oxLDL), the autoimmune response to apolipoprotein B (apoB) peptides-derived from an LDL particle was determined. Previous studies showed that antibodies against a specific peptide (ApoB-D) can be considered a marker of inflammatory activation.[5-7] However, it has not been shown that chronic infection can modulate the autoantibodies (Abs) into auto-antigens, especially in the immune system deficiency condition.

Materials and methods

Subjects

This study conducted a cross-sectional, case-control, pilot study including prospectively 40 HIV-infected subjects, naïve for highly active antiretroviral therapy (HAART) for both genders. Fifty-three HIV non-infected subjects (control) were recruited from the same communities, using the same advertisements and cardiovascular risk factors. After blood collections and clinical evaluations, HIV-infected patients who began HAART therapy adhered to the prescribed medications.

Lipids and biochemical analysis

Serum total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides were determined enzymatically (Opera Bayer, Leverkusen, Germany) with low-density lipoprotein cholesterol (LDL-C), estimated by the *Friedewald* equation when triglycerides were <400 mg/dl.[8] Glucose was evaluated by the enzymatic method.

Endothelial function and carotid intima-media thickness

Ultrasound tests were performed to evaluate the subclinical atherosclerosis by carotid intimal medial-thickness (cIMT)[9] and vasoreactivity assessment of endothelial-dependent flow-mediated dilation (FMD) of the brachial artery.[10]

Mailing Address: Henrique Andrade Fonseca •
Universidade Federal de São Paulo Escola Paulista de Medicina - Rua Loefgreen, 1350. Postal Code 04023-062, Vila Clementino, São Paulo, SP - Brazil
E-mail: har.fonseca@yahoo.com.br
Manuscript received January 26, 2020, revised mansucript April 23, 2020, accepted June 16, 2020

DOI: https://doi.org/10.36660/abc.20200062

Briefly, patients were required to fast and abstain from nitrates, alcohol, and vasoactive medications for 24 h prior to the tests. After a 15-20 min rest, the brachial artery in the right antecubital fossa was viewed, using a linear transducer with a frequency of up to 11 MHz, together with simultaneous monitoring by means of an electrocardiogram (ECG). Images were obtained by HP SONOS 5500 ultrasound system (Hewlett Packard, Palo Alto, USA). Once the optimal image of the artery was achieved, the baseline vessel diameter was measured. Reactive hyperemia was induced by inflating the blood pressure cuff to 200 mmHg, or at least 50 mmHg above SBP, on the distal forearm for 5 min and then deflating the cuff. End-diastolic images were obtained at the time of onset of the QRS complex on ECG. These images were acquired at baseline and one min after cuff deflation. The percentage change from the baseline diameter to the value detected during reactive hyperemia was calculated to determine the FMD. The FMD and cIMT measurements were evaluated by an experienced sonographer in a blinded fashion. The intra-sonographer and inter-sonographer variability were less than 1% and 2%, respectively.

Cytokines and CD4 T-cells

Cytokine concentrations were tested using commercially available ELISA kits. Plasma viral load and CD4 T-cell counts were determined for HIV-infected subjects. The nadir CD4+ T-cell count was defined as the lowest registered and laboratory-confirmed value.

Autoantigen isolation and synthesis

The LDL particle was obtained from total plasma after centrifugation (1,000 g; 4 °C; 15 min) and supplemented with benzamidine (2 mM), gentamicin (0.5%), chloramphenicol (0.25%), phenylmethylsulfonyl fluoride (PMSF) (0.5 mM), and aprotinin (0.1 unit/mL). Low-density lipoprotein particles ($1.006<d<1.063$ mg/mL) were isolated by sequential ultracentrifugation (100,000 g; 4 °C), using a rotor (70 Ti, fixe angle; Beckman Coulter, USA) and an ultracentrifuge (Hitachi, Japan). The LDL particle was copper-oxidized and used as an autoantigen to evaluate autoantibodies titers.[11] The apolipoprotein B-peptides (apoB-peptides) used in this study consisted of two synthetic fragments: ApoB-D (ApoB-D, which is an ApoB-peptide fragment with a 22-amino-acid sequence derivate of domain 3 of the apolipoprotein B sequence in the third conserved portion for tripsin digestions)[12] and peptide-0033G-Cys (peptide-0033G-Cys, which is a peptide fragment with a 21-amino-acid derivate of domain 3 of the apolipoprotein B sequence in the first conserved portion for trypsin digestion).[12]

Determinations of autoantibodies

The quantification of oxLDL and apoB-peptide derivate autoantibodies (Abs) was assessed in total plasma by ELISA, as previously described.[13,14] Ninety-six-well microtiter plates (Microplates 8096, Costar-USA) were coated with 10μg/mL of the ApoB-D or 0033G-Cys peptide in carbonate/bicarbonate buffer (0.1 mol/l; pH 9.6), which was left for sensitization overnight at 4ºC. After three cycles of washing with phosphate buffered saline (PBS, pH 7.4) plus Tween-20 (0.05%), the plate was blocked with gelatin (3%; room temperature; 24 h). Patients' plasma samples (50 μl/well, 1:400 in phosphate buffer, PBS, pH 7.4) were added to the plates for 2 hours at room temperature. Next, three more cycles of washing were performed, and secondary IgG horseradish peroxidase-conjugated antibodies (purified goat anti-human IgG, 0.1 μg/ml, KPL, Kirkegaard & Perry Laboratories, Gaithersburg, Maryland, USA) or IgM (purified goat anti-human IgM, 10 μg/ml KPL, Kirkegaard & Perry Laboratories, Gaithersburg, Maryland, USA) were added to evaluate the titers of anti-ApoB-D or anti-0033G-Cys peptide Abs. After incubation (1 hour), the plaques were washed (three cycles), and 3,3,5,5-tetramethylbenzidine (6.5% in dimethyl sulfoxide; Sigma, St Louis, MO) and H_2O_2 (Sigma) diluted in citrate/phosphate buffer (0.1mol/l; 250μl; pH 5.5) were added (room temperature), as enzyme substrates. The reaction was stopped by adding H_2SO_4 (2mol/l). The optical density (OD) of samples was measured at 450 nm. Autoantibodies (Abs) titers were expressed as the reactivity index (RI), calculated as $RI=(OD_{sample} - OD_{sample\ blank}) / (OD_{IgG\ or\ IgM} - OD_{IgG\ or\ IgM\ blank})$ where the IgG or IgM antibodies were used as controls. The intra-assay coefficient of variation was 5.4% and the intra-assay was 2.0%.

Anti-oxLDL Abs titers were performed similarly to the apolipoprotein B peptide assay but using ninety-six-well microtiter plates coated with 7.5 μg/ml of oxLDL.[13] The total antibodies were determined in total plasma by the ELISA method.

Samples were run in triplicate and the variation within the triplicates did not exceed 5% of the mean.

Ethics

The study was approved by the institutional ethics committee of the Federal University of São Paulo and University of São Paulo (FO. 99/2009), and written informed consent was obtained from all participants prior to beginning the protocol.

Statistical analysis

Statistical analyses were performed using the SPSS 17.0 software package (Statistical Package for Social Science, SPSS Inc., Chicago, IL, USA). Categorical variables were compared by Pearson's chi-square test. Distribution of normality was assessed by the Kolmogorov-Smirnov test. Between group analyses were tested by a *t* test or Mann-Whitney test. Interaction between endothelial function and other variables were tested by Pearson or Spearman tests. Variables identified to have significant interaction were tested with stepwise multiple linear regression analyses, with an endothelial function as a dependent variable. A significance level of 5% was used for all tests.

Results

Clinical and demographic parameters are presented in Table 1. There were no differences in the cIMT among

HIV-infected and non-infected subjects. The endothelial function was decreased in HIV-infected subjects (p=0.040). (Table 1).

As expected, HIV-infected subjects had significantly higher inflammatory marker levels than did non-infected individuals; however, the anti-inflammatory cytokine IL-10 did not differ between the groups (Table 1).

Serum total IgG and IgM Abs titers did not differ among HIV-infected and uninfected subjects (Table 1). Figure 1 demonstrated that titers of IgG anti-oxLDL Abs were higher in HIV-infected subjects (p<0.001). However, the titers of IgM anti-oxLDL Abs did not differ among HIV-infected and uninfected subjects. HIV-infected subjects had higher titers of IgG anti-ApoB-D Abs (p<0.001) and lower titers of IgM anti-ApoB-D when compared to non-infected subjects (p=0.040). No differences were observed among groups for the anti-peptide-0033G-Cys Abs.

The present study showed that in HIV-infected subjects the endothelial function was associated with IgM anti-ApoB-D Abs titers [β=10.75; p=0.015] (Table2). The stepwise regression model, including traditional cardiovascular risk factors, HIV-related markers, and immune responses showed that IgM anti-ApoB-D Abs were associated with the endothelial function [β=7.28; p=0.002]. Associations among IgG anti-ApoB-D and the endothelial function were not observed. Regarding subclinical atherosclerosis, the cIMT measures were not associated with the humoral response for both peptides.

Discussion

The present study showed that, in HIV-infected subjects, naïve of antiretroviral therapy, a reduced endothelial function accompanies distinct modulation in Abs against apoB-peptides fragments, as compared to non-infected subjects, regardless of serum total Abs titers.

Data related to humoral immunity and apoB peptides suggest that their presence is associated with atherosclerotic disease progression, as part of an autoimmune response.[5,14] However, these Abs can participate in the clearance of pro-atherogenic products generated from the oxidation of LDL particles and the modification of apoB, performing a dual role in the atherogenesis process.[15,16]

This study also showed that IgM Abs against ApoB-D were associated with ED, corroborating with previous studies.[6,17] Our findings suggest that there is a clearance of apoB autoantigens by natural antibodies, suggesting that they may be involved in vascular repair after an injury process,[18] however the effects of HIV infection on FMD may be attributable to a distinct stage of disease and distinct drug therapies adopted.[19]

Cohort studies and meta-analysis showed that cIMT in HIV-infected, when compared to non-infected, subjects is higher.[20] We believe the time of infection in our study was not enough to promote carotid atherosclerosis modification detected by an ultrasound exam.

The present study's results suggest that autoantibodies to defined-apoB peptides can be a marker of endothelial dysfunction, or even of an elevated inflammatory response, but not of carotid atherosclerosis in HIV-infected patients. Cohort and clinical trials with patients submitted to HARRT merit further investigation to confirm these preliminary results.

The cross-sectional design and the lack of a group receiving antiretroviral therapy for comparisons of the effects of HAART drugs on endothelial function and subclinical atherosclerosis are a limitation. No significant differences were found among sex groups, which may be justified by the small number of subjects included in this study. Additional studies, including a larger number of patients, are needed to confirm our findings related to sex, infection, and endothelial function. For adjustments, the effects of different cardiovascular risk factors and infection markers were evaluated as a possible explanation for the observed natural immune response associated with the vascular function.

Conclusion

This study's findings suggest that natural immunity to apoB antigens is associated with ED. Further prospective studies for the evaluation of HIV immunological parameters in autoimmune response and these effects on vascular function are warranted.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Fonseca HA, Gidlund M, Fonseca FAH, Izar MC; Data acquisition: Fonseca HA, Fernandes ER; Analysis and interpretation of the data: Fonseca HA, Gidlund M, Sant'Anna VR, Fernandes ER; Statistical analysis: Fonseca HA, Sant'Anna VR; Obtaining financing: Fonseca HA, Fonseca FAH; Writing of the manuscript: Fonseca HA, Gidlund M, Sant'Anna VR, Izar MC.

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.

Sources of Funding

There was no external funding source for this study.

Study Association

This study is not associated with any thesis or dissertation.

Table 1 – Characteristics of the HIV naïve infected and uninfected subjects

Variables	Overall (93)	HIV- (Control) (53)	HIV+ (Naïve) (40)	p-values
Clinical parameters				
Gender (males/females)	63/30	32/21	31/9	0.110
Age (years)	32 (1.0)	32 (1.7)	32 (1.3)	0.746
Abdominal circumference (cm)	88 (83-97)	89.5 (76.5-100)	97 (83-96)	0.668
Body mass index (kg/m²)	24.8 (23-28)	25.5 (21.5-28.5)	25.2 (23.5-28)	0.586
Smokers (%)	11	6	5	0.951
Systolic blood pressure (mmHg)	120 (110-120)	120 (110-120)	120 (110-120)	0.631
Diastolic blood pressure (mmHg)	80 (70-80)	80 (70-80)	80 (70-80)	0.441
Biochemical analysis				
Total cholesterol (mg/dL)	165 (139-185)	166 (144-191)	150 (124-176)	0.028
LDL-c (mg/dL)	98 (69-115)	103 (77-119)	91 (66-113)	0.095
HDL-c (mg/dL)	46 (37-65)	47 (40-57)	36 (30-46)	0.008
Triglycerides (mg/dL)	91 (52-122)	88 (67-131)	113 (73-131)	0.285
Glucose (mg/dL)	90 (86-94)	90 (86-94)	92 (86-96)	0.425
HIV parameters of infection				
Time of infection (years)	-	-	3 (1-6)	N.A
CD4 count (cells/μL)	-	-	447 (366-590)	N.A
CD4 nadir (cells/μL)	-	-	402 (356-537)	N.A
HIV viral load (RNA copies/μL)	-	-	2623 (485-26225)	N.A
HBV coinfection	0	0	4	N.A
HCV coinfection	0	0	3	N.A
Therapies in use				
Antihypertensive (individuals, *N*)	4	3	1	N.A
Statins (individuals, *N*)	0	0	0	N.A
Neurological drugs (individuals, *N*)	3	2	1	N.A
Inflammatory markers				
hs-CRP (mg/L)	1.20 (0.30-1.92)	0.51 (0.20-1.87)	1.48 (0.82-3.30)	0.017
IFN-γ (pg/dL)	2.84 (0.90-6.85)	1.43 (0.87-4.10)	3.89 (1.30-8.85)	0.021
TNF-α (pg/dL)	6.66 (5.58-7.31)	6.02 (5.51-6.94)	6.90 (6.54-7.63)	0.020
IL-6 (pg/dL)	1.54 (1.37-1.80)	1.54 (1.36-1.63)	1.50 (1.37-1.95)	0.028
IL-8 (pg/dL)	3.13 (2.50-4.60)	2.80 (2.20-4.40)	3.65 (2.70-5.50)	0.050
IL-10 (pg/dL)	1.75 (0.39-1.97)	1.79 (0.80-1.98)	0.87 (0.36-1.94)	0.088
Total antibodies				
IgG total serum (RI)	1.33 (1.19-1.38)	1.34 (1.20-1.38)	1.33 (1.18-1.37)	0.877
IgM total serum (RI)	0.69 (0.55-0.84)	0.67 (0.49-0.82)	0.73(0.58-0.86)	0.310
Subclinical atherosclerosis				
Intima-media Thickness (mm)	0.67 (0.57-0.68)	0.67 (0.56-0.68)	0.67 (0.57-0.68)	0.971
Endothelial function				
Flow-mediated Dilatation (%)	11.6 (1.4)	13.7 (2.4)	9.3 (1.2)	0.040

HBV: hepatitis B virus; HCV: hepatitis C virus; N.A: not applicable; RI: reactivity index.

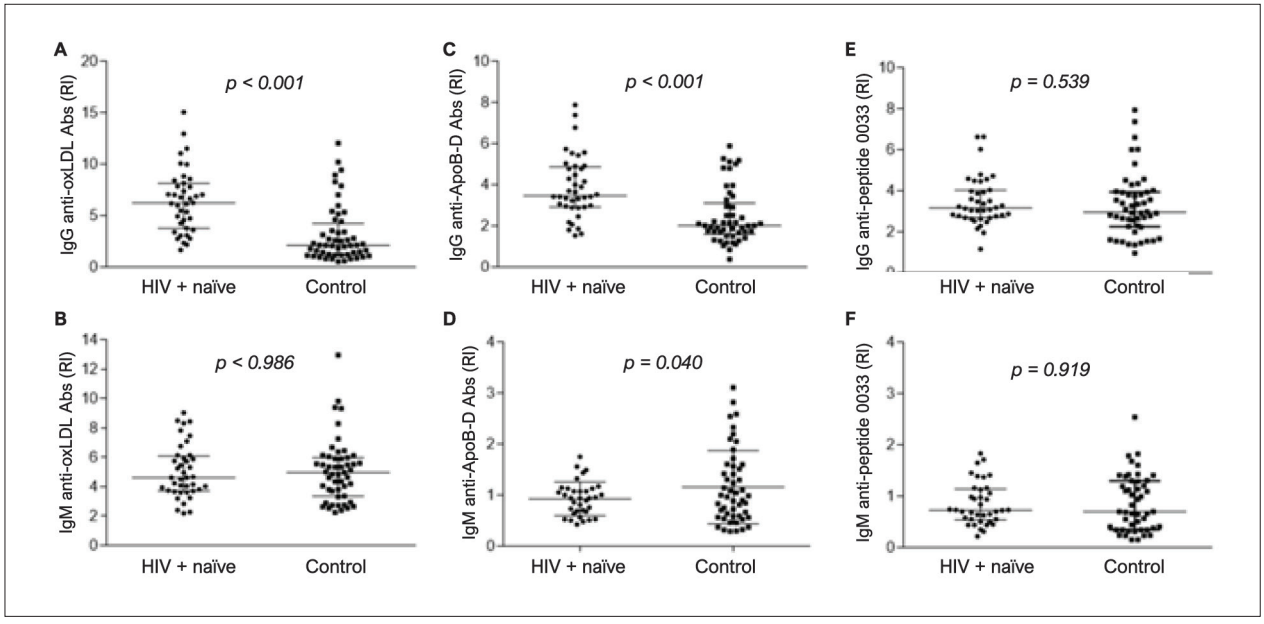


Figure 1 - *Humoral response to oxidized LDL, ApoB-D peptide and 0033-peptide in HIV-infected patients and non-infected controls. (A) IgG anti-oxLDL autoantibodies (Abs); (B) IgM anti-oxLDL Abs; (C) IgG anti-ApoB-D peptide Abs; (D) IgM anti-ApoB-D Abs. (E) IgG anti-0033-peptide Abs; (F) IgM anti-0033-peptide. Significant differences between groups were calculated by the Mann-Whitney test.*

Table 2 – Univariate adjusted analysis of potential risk factors associated with endothelial function in HIV-infected subjects

Variables	β	p-values
Age (years)	-0.187	0.350
Abdominal circumference	-0.049	0.708
IgM anti-ApoB-D peptide	10.754	0.015
IgG anti-ApoB-D peptide	0.597	0.351
Nadir CD4	0.007	0.135
Current CD4	-0.010	0.126
Log viral load	0.413	0.786
Time of infection	-0.215	0.718

β-coefficient represent the changes in the percentage of flow-mediated dilatation for the predictor variables. Adjustments were made for hypertension, current smoking, and dyslipidemia. CI: Confidence interval.

References

1. Feinstein MJ, Hsue PY, Benjamin LA, Bloomfield GS, Currier JS, Freiberg MS, et al. Characteristics, prevention, and management of cardiovascular disease in people living with HIV: a scientific statement from the American Heart Association. Circulation. 2019;140(2):e98-124.
2. Kearns A, Gordon J, Burdo TH, Qin X. HIV-1-Associated atherosclerosis: unraveling the missing link. J Am Coll Cardiol. 2017;69(25):3084-98.
3. Stein JH, Currier JS, Hsue PY. Arterial disease in patients with human immunodeficiency virus infection: what has imaging taught us? JACC Cardiovasc Imaging. 2014;7(5):515-25.
4. Pocock MO, Dorrell L, Cicconi P. Pathophysiology of ischaemic heart disease. Curr Opin HIV AIDS. 2017;12(6):548-53.
5. Fonseca HAR, Fonseca FA, Monteiro AM, Bianco HT, Boschcov P, Brandão SA, et al. Obesity modulates the immune response to oxidized LDL in hypertensive patients. Cell Biochem Biophys. 2013;67(3):1451-60.
6. Fonseca HAR, Fonseca FA, Lins LC, Monteiro AM, Bianco HT, Brandão SA, et al. Antihypertensive therapy increases natural immunity response in hypertensive patients. Life Sci. 2015 Dec 15;143:124-30.
7. Svensjö, Boschcov P, Ketelhuth DF, Jancar S, Gidlunf M. Increased microvascular permeability in the hamster cheek pouch induced by oxidized low density lipoprotein (oxLDL) and some fragmented apolipoprotein B proteins. Inflamm Res. 2003;52:215-20.

8. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18(6):499-502.

9. Stein JH, Korcarz CE, Hurst RT, Lonn E, Kendall CB, Mohler ER, et al. American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Use of carotid ultrasound to identify subclinical vascular disease and evaluate cardiovascular disease risk: a consensus statement from the American Society of Echocardiography Carotid Intima-Media Thickness Task Force. Endorsed by the Society for Vascular Medicine. J Am Soc Echocardiogr. 2008;21(2):93-111.

10. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery. a report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol. 2002;39(2):257-65.

11. Fernvik EC, Ketelhuth DF, Russo M, Gidlund M. The autoantibody repertoire against copper- or macrophage-modified LDL differs in normolipidemics and hypercholesterolemic patients. J Clin Immunol. 2004;24(2):170-6.

12. Yang CY, Gu ZW, Weng SA, Kim TW, Chen SH, Pownall HJ, et al. Structure of apolipoprotein B-100 of human low density lipoproteins. Arteriosclerosis. 1989;9(1):96-108.

13. Fonseca HAR, Fonseca FAH, Monteiro AM, Farias Jr NC, Bianco HT, Brandão SAB, et al. Inflammatory environment and immune responses to oxidized LDL are linked to systolic and diastolic blood pressure levels in hypertensive subjects. Int J Cardiol. 2012;157(1):131-3.

14. Soares SR, Carvalho-Oliveira R, Ramos-Sanchez E, Catazoni S, Silva LFF, Mauad T, et al. Air pollution and antibodies against modified lipoproteins are associated with atherosclerosis and vascular remodeling in hyperlipemic mice. Atherosclerosis. 2009;207(2):368-73.

15. Lopes-Virella MF, Virella G. Pathogenic role of modified LDL antibodies and immune complexes in atherosclerosis. J Atheroscler Thromb. 2013;20(10):743-54.

16. Ronchini KR, Duarte AJ, Casseb JSR, Gidlund M. Cardiovascular complications and increased levels of circulating modified low density lipoprotein in HIV patients and patients with lipodystrophy. Braz J Med Biol Res. 2004;37(1):119-22.

17. Orellana RV, Fonseca HA, Monteiro AM, Ortega KL, Gallottini MH, Gidlund M, et al. Association of autoantibodies anti-OxLDL and markers of inflammation with stage of HIV infection. Int J Cardiol. 2013;168(2):1610-2.

18. Asciutto G, Wigren M, Fredrikson GN, Mattisson IY, Grönberg C, Alm R, et al. Apolipoprotein B-100 antibody interaction with atherosclerotic plaque inflammation and repair processes. Stroke. 2016;47(4):1140-3.

19. Bush KNV, Teel JL, Watts JA, Gore RS, Alvarado G, Harper NL, et al. Association of endothelial dysfunction and antiretroviral therapy in early HIV infection. JAMA Netw Open. 2019;2(10):e1913615.

20. Wohl DA, Arnoczy G, Fichtenbaum CJ, Campbell T, Taiwo B, Hicks C, et al. Comparison of cardiovascular disease risk markers in HIV-infected patients receiving abacavir and tenofovir: the nucleoside inflammation, coagulation and endothelial function (NICE) study. Antivir Ther. 2014;19(2):141-7.

Transthyretin Amyloid Cardiomyopathy Mimicking Hypertrophic Cardiomyopathy in an Older Patient

José Pedro Alves Guimarães,[1] Joana Trigo,[1] Fernando Gonçalves,[1] J. Ilídio Moreira[1]

Centro Hospitalar de Trás-os-montes e Alto Douro EPE – Cardiologia,[1] Vila Real – Portugal

Wild-type transthyretin amyloid cardiomyopathy (wt-ATTR-CM) is increasingly recognized due to the recognition of the increasing prevalence, advances in diagnostic methods, and the development of effective treatments.

We report the case of an 88-year-old female with history of hypertension, chronic kidney disease (CKD), heart failure with preserved ejection fraction, and no relevant family history. She presented to the emergency department with history of syncope, productive cough, worsening dyspnea, and fever. The auscultation showed a grade III/VI systolic murmur in her left sternal border, no breath sounds in the right lung base and bilateral rhonchi.

The electrocardiogram revealed a complete atrioventricular (AV) block; the chest X-ray, a bilateral alveolar edema and consolidation in the right lung, and the analytical results were remarkable for acute kidney injury with hyperkalemia. The AV block resolved after potassium levels correction, and she was admitted with the diagnosis of community acquired pneumonia and decompensated heart failure.

The transthoracic echocardiogram (Video 1) revealed asymmetric hypertrophy of the left ventricle (Figure 1 - A and B) and systolic anterior motion of the mitral valve causing obstruction of the left ventricle outflow tract (LVOT) with mid-systolic closure of the aortic valve (Figure 1 - C and D). These findings were suggestive of hypertrophic cardiomyopathy (HCM). The LV was non-dilated and had a preserved ejection fraction; her global longitudinal strain (GLS) was reduced with an apical sparing pattern (Figure 2). There was moderate mitral regurgitation, mild aortic regurgitation, and the estimated systolic pulmonary artery pressure was 40 mmHg.

The ^{99m}Tc-DPD *scintigraphy showed diffuse biventricular tracer uptake (grade II, Figure 3), and there was* no evidence of a monoclonal protein in serum and urine immunofixation and in a light chain essay.

The echocardiographic features, the cardiac uptake of ^{99m}Tc-DPD, and the absence of a monoclonal protein defined the diagnosis of ATTR-CM.

Unfortunately, the patient had an unfavorable outcome with a nosocomial superinfection and progressive heart failure that culminated in death. The results of the TTR genetic testing were negative, thus confirming the diagnosis of wt-ATTR.

Wt-ATTR may be the most frequent form of cardiac amyloidosis,[1] however the diagnosis is challenging given the broad clinical spectrum, lack of "classical" findings, and the phenotype attributed to hypertensive heart disease, aortic stenosis, or HCM.

Echocardiography is the diagnostic cornerstone and the main finding is LVH, but the ratio of patients with asymmetric LVH is high.[2] Strain imaging is useful for the differential diagnosis because of its distinctive pattern of "apical sparing".[3] Other signs are valve thickening, atrial septal thickening, right ventricular hypertrophy, biatrial dilatation, mild pericardial effusion, and granular sparkling appearance of the myocardium.[4]

Nuclear scintigraphy using bone tracers is useful for the non-invasive diagnosis. Grade II or III uptake in the absence of a monoclonal protein had 100% specificity and positive predictive value in a landmark study.[5] Because light-chain amyloidosis can cause mild cardiac uptake and unrelated monoclonal gammopathy is common in older patients, screening for a monoclonal protein is mandatory. Finally, genetic testing is required to distinguish between wt and hereditary-ATTR.[4]

ATTR-CM is an under-recognized cause of heart failure in older adults. With the development of effective therapies, the appropriate recognition and diagnosis of ATTR-CM will have a direct therapeutic impact.

Author contributions

Conception and design of the research, Acquisition of data and Writing of the manuscript: Guimarães JPA; Critical revision of the manuscript for intellectual content: Trigo J, Gonçalves F, Moreira JI.

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

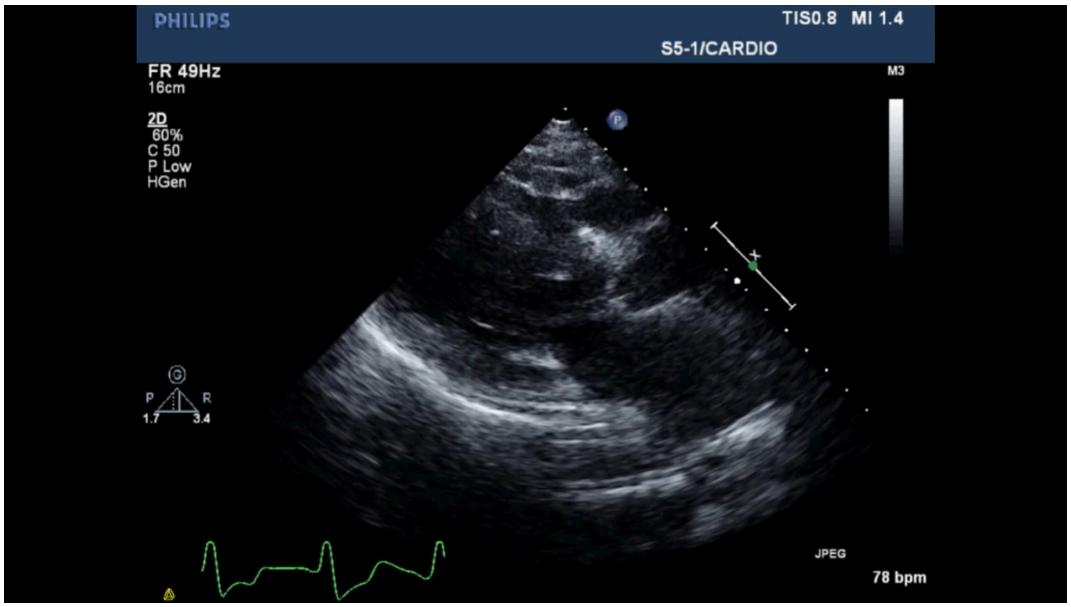
This article does not contain any studies with human participants or animals performed by any of the authors.

Keywords

Amyloidosis; Cardiomyopathy, Hypertrophic; Hypertension; Heart Failure; Stroke; Renal, Insufficiency Chronic; Echocardiography/methods.

Mailing Address: José Pedro Alves Guimarães •
Centro Hospitalar de Trás-os-montes e Alto Douro EPE – Cardiologia – Av. Noruega Vila Real 5000-508 – Portugal
E-mail: josepedro.ag@gmail.com
Manuscript received February 13, 2020, revised manuscript March 24, 2020, accepted April 22, 2020

DOI: https://doi.org/10.36660/abc.20200236



Video 1 – *Transthoracic echocardiogram parasternal and apical views. Valve (red arrow) (C-D) with a maximum intraventricular gradient of 70 mmHg. URL: http://abccardiol.org/supplementary-material/2021/11604/2020-0236-video01.mp4*

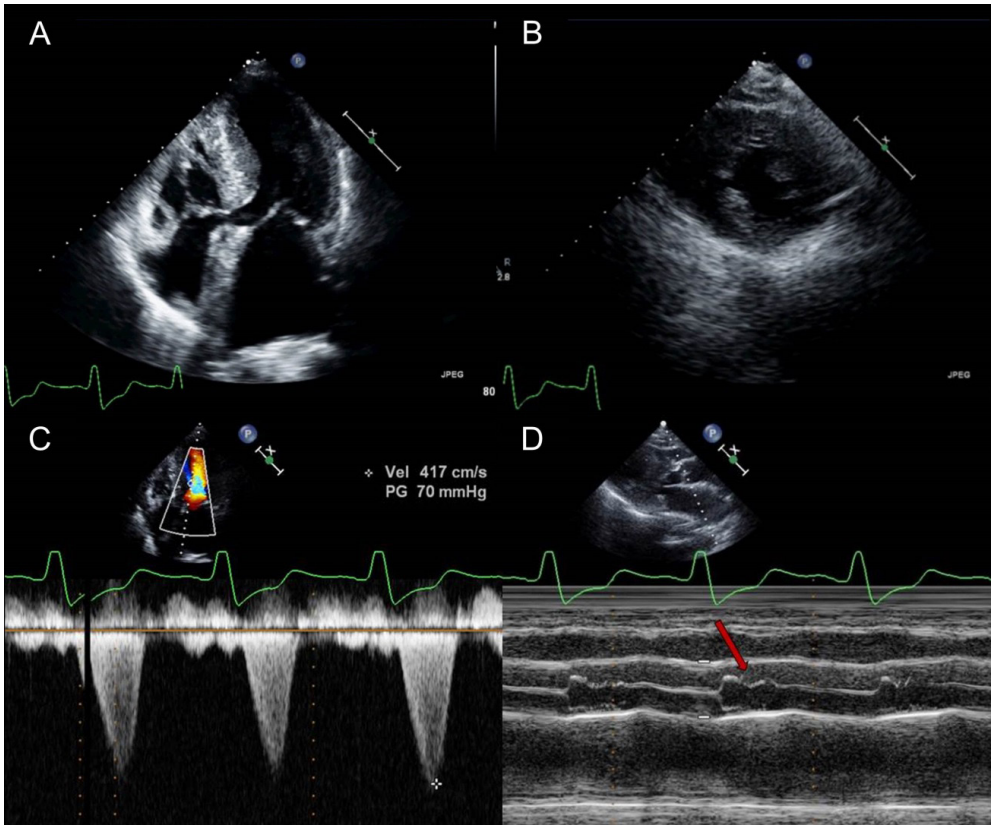


Figure 1 – *Asymmetric septal hypertrophy (septum=19mm; posterior wall=13mm) (A-B); systolic anterior motion of the mitral valve causing LVOT and mid-systolic closure of the aortic valve.*

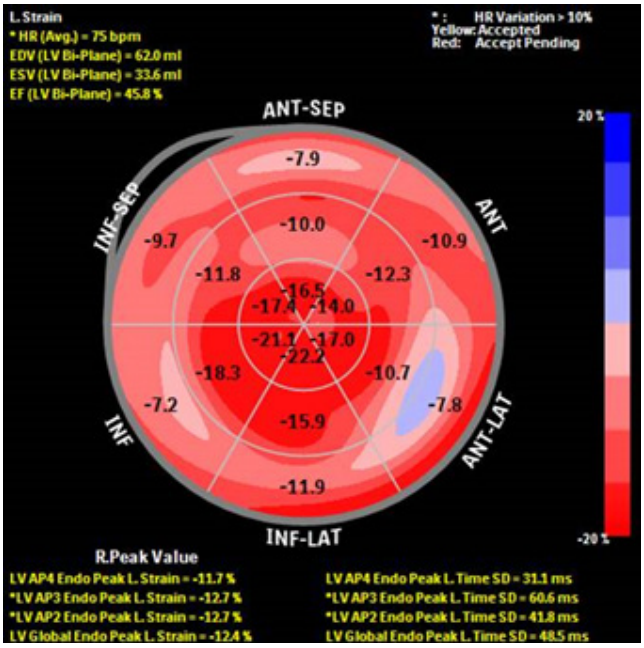


Figure 2 – *Reduced GLS (-12.4%) and relative apical sparing pattern.*

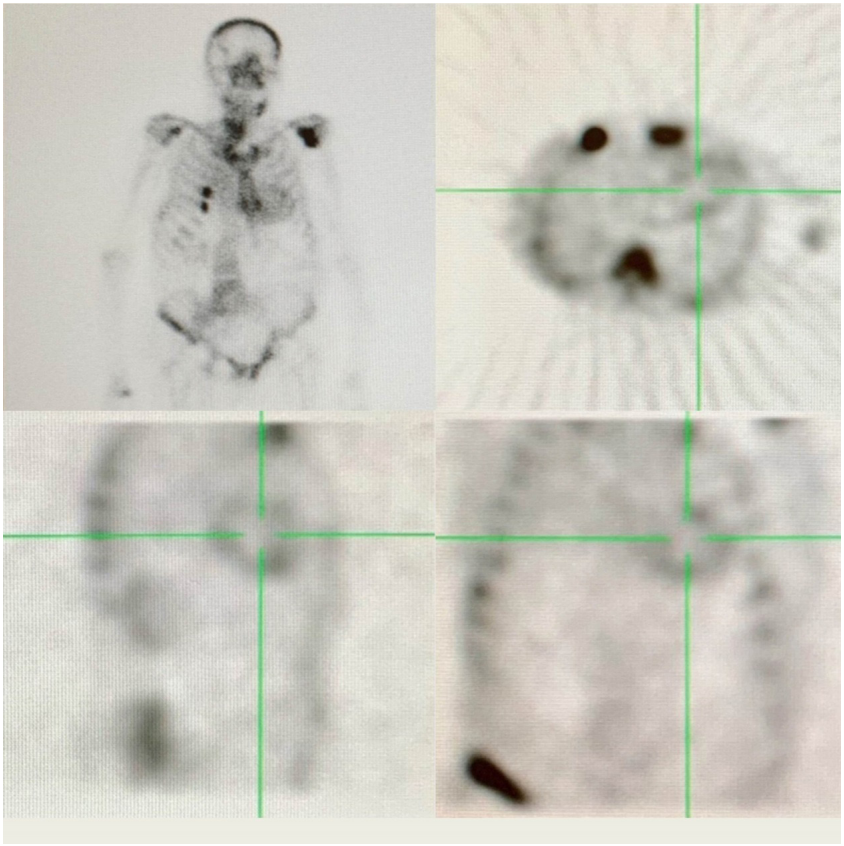


Figure 3 – *^{99m}Tc-DPD scintigraphy showing grade II biventricular tracer uptake.*

References

1. Gilstrap L G, Francesca D, Yun W, El-Sady MS, Amitoj S, Di Carli MF. et al. Epidemiology of Cardiac Amyloidosis–Associated Heart Failure Hospitalizations Among Fee-for-Service Medicare Beneficiaries in the United States. Circ Heart Fail. 2019 Jun 1;12(6):e005407.
2. Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS, et al. Magnetic Resonance in Transthyretin Cardiac Amyloidosis. J Am Coll Cardiol. 2017 Jul 25;70(4):466–77.
3. Pagourelias ED, Mirea O, Duchenne J, Van Cleemput J, Delforge M, Bogaert J, et al. Echo Parameters for Differential Diagnosis in Cardiac Amyloidosis: A Head-to-Head Comparison of Deformation and Nondeformation Parameters. Circ Cardiovasc Imaging. 2017 Mar;10(3):e005588.
4. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin Amyloid Cardiomyopathy. J Am Coll Cardiol. 2019 Jun 11;73(22):2872.
5. Gillmore JD, Maurer MS, Falk RH,, Merlini G, Damy Thibaud, Dispenzieri A, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation. 2016 Jun 14;133(24):2404–12.

Troponin-T and B-Type Natriuretic Peptide in COVID-19

Sora Yasri[1] *and Viroj Wiwanitkit*[1]
Dr. DY Patil University, Pune - India

Dear Editor,

We would like to share ideas on the publication "Prognostic Value of Troponin-T and B-Type Natriuretic Peptide in Patients Hospitalized for COVID-19 [1]." Almeida Jr. et al.[1] reported using Memory box as a tool to support grief and concluded that "*In the first 24h of admission, TnT, but not BNP, was an independent marker of mortality or need for invasive mechanical ventilation.*"[1] In COVID-19, cardiac complication is possible and is common in severe infection.[2] Myocardial involvement is a common cardiac problem and immunological myocarditis is an important severe manifestation of COVID-19.[3] Therefore, troponin-T, which is a good biomarker for myocardial injury, might have good prognostic factor for severity of COVID-19. Nevertheless, it should be noted that renal problems can also induce troponin-T abnormality.[4] If the patient has an underlying renal problem, the interpretation of troponin-T in COVID-19 patients must be careful.

Keywords

COVID-19/complications; Betacoronavirus; Mortality; Hospitalization; Myocarditis; Biomarkers; Troponi-T; Natriuretic B-Type

Mailing Address: Sora Yasri •
Private Academic Practice Bangkok 1-2012021 – Tailândia
E-mail: sorayasri@outlook.co.th
Manuscript received November 09, 2020, revised manuscript December 16, 2020, accepted December 16, 2020

DOI: https://doi.org/10.36660/abc.20201191

References

1. Almeida Junior GLG, Braga F, Jorge JK, Nobre GF, Kalichsztein M, Faria PMP, et al. Prognostic Value of Troponin-T and B-Type Natriuretic Peptide in Patients Hospitalized for COVID-19. Arq Bras Cardiol. 2020 Oct;115(4):660-6.
2. Guo T, Fan Y, Chen M, Wu X, Zhang L, He T, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). JAMA Cardiol. 2020 Jul 1;5(7):811-8
3. Kogan EA, Berezovskiy YS, Blagova OV, Kukleva AD, Bogacheva GA, Kurilina EV, et al. Miocarditis in Patients with COVID-19 Confirmed by Immunohistochemical. Kardiologiia. 2020 Jun 19;60(7):4-10.
4. Bozbas H, Yildirir A, Muderrisoglu H. Cardiac enzymes, renal failure and renal transplantation. Clin Med Res. 2006 Mar;4(1):79-84.

Erratum

October 2019 Issue, vol. 113 (4), pages 787-891

In the "Updated Cardiovascular Prevention Guideline of the Brazilian Society of Cardiology – 2019", with DOI: https://doi.org/10.5935/abc.20190204, published in the journal Arquivos Brasileiros de Cardiologia, on page 862, correct item "Non-HDL-cholesterol" in table 11.3, "> 145" to "<145", in columns 1 and 2; on page 863, correct the item "Non-HDL-cholesterol", in Lipids, from table 11.6, "> 145" to "< 145", in columns 1 and 2.

January 2021 Issue, vol. 116 (1), pages 160-212

In the "Position Statement on Fat Consumption and Cardiovascular Health – 2020", with DOI: https://doi.org/10.36660/abc.20201340, published in the journal Arquivos Brasileiros de Cardiologia, 116(1):160-212, on page 160, correct author name Lis Mie Misuzawa Beda to: Lis Mie Masuzawa Beda.

DOI: DOI: https://doi.org/10.36660/abc.20210278