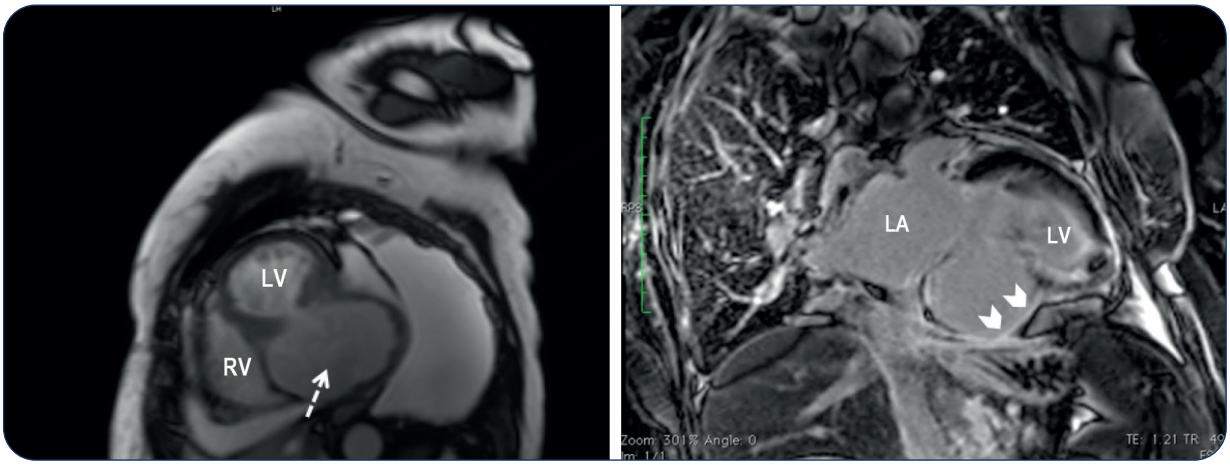
ABC Cardiol
Journal of Brazilian Society of Cardiology

Volume 114 | Number 4
April 2020

Brazilian Society of Cardiology
ISSN-0066-782X



Figures 3 and 4 da Page 731.

Chief Editor
Carlos Rochitte

Internacional Coeditor
João Lima

Editors
Gláucia Moraes
Alexandre Colafranceschi
Ieda Jatene
João Cavalcante
Marcio Bittencourt
Marina Okoshi
Mauricio Scanavacca
Paulo Jardim
Pedro Lemos
Ricardo Stein
Tiago Senra
Vitor Guerra

ABC Cardiol
Journal of Brazilian Society of Cardiology

JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

Contents

ABC Cardiol
Journal of Brazilian Society of Cardiology

JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

Scientific Director
Fernando Bacal

Chief Editor
Carlos Eduardo Rochitte

International Co-editor
João Lima

Associated Editors

Clinical Cardiology
Gláucia Maria Moraes de Oliveira

Surgical Cardiology
Alexandre Siciliano Colafranceschi

Interventionist Cardiology
Pedro A. Lemos

Pediatric/Congenital Cardiology
Ieda Biscegli Jatene

Vitor C. Guerra

Arrhythmias/Pacemaker
Mauricio Scanavacca

Non-Invasive Diagnostic Methods
João Luiz Cavalcante

Basic or Experimental Research
Marina Politi Okoshi

Epidemiology/Statistics
Marcio Sommer Bittencourt

Arterial Hypertension
Paulo Cesar B. V. Jardim

Ergometrics, Exercise and Cardiac Rehabilitation
Ricardo Stein

First Editor (1948-1953)
† Jairo Ramos

Editorial Board

Brazil

Aguinaldo Figueiredo de Freitas Junior – Universidade Federal de Goiás (UFG), Goiânia GO – Brazil

Alfredo José Mansur – Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, SP – Brazil

Aloir Queiroz de Araújo Sobrinho – Instituto de Cardiologia do Espírito Santo, Vitória, ES – Brazil

Amanda Guerra de Moraes Rego Sousa – Instituto Dante Pazzanese de Cardiologia/Fundação Adib Jatene (IDPC/FAJ), São Paulo, SP – Brazil

Ana Clara Tude Rodrigues – Hospital das Clinicas da Universidade de São Paulo (HCFMUSP), São Paulo, SP – Brazil

André Labrunie – Hospital do Coração de Londrina (HCL), Londrina, PR – Brazil

Andrei Carvalho Sposito – Universidade Estadual de Campinas (UNICAMP), Campinas, SP – Brazil

Angelo Amato Vincenzo de Paola – Universidade Federal de São Paulo (UNIFESP), São Paulo, SP – Brazil

Antonio Augusto Barbosa Lopes – Instituto do Coração Incor Hc Fmusp (INCOR), São Paulo, SP – Brazil

Antonio Carlos de Camargo Carvalho – Universidade Federal de São Paulo (UNIFESP), São Paulo, SP – Brazil

Antônio Carlos Palandri Chagas – Universidade de São Paulo (USP), São Paulo, SP – Brazil

Antonio Carlos Pereira Barretto – Universidade de São Paulo (USP), São Paulo, SP – Brazil

Antonio Cláudio Lucas da Nóbrega – Universidade Federal Fluminense (UFF), Rio de Janeiro, RJ – Brazil

Antonio de Padua Mansur – Faculdade de Medicina da Universidade de São Paulo (FMUSP), São Paulo, SP – Brazil

Ari Timerman (SP) – Instituto Dante Pazzanese de Cardiologia (IDPC), São Paulo, SP – Brazil

Armênio Costa Guimarães – Liga Bahiana de Hipertensão e Aterosclerose, Salvador, BA – Brazil

Ayrton Pires Brandão – Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, RJ – Brazil

Beatriz Matsubara – Universidade Estadual Paulista Júlio de Mesquita Filho (UNESP), São Paulo, SP – Brazil

Brivaldo Markman Filho – Universidade Federal de Pernambuco (UFPE), Recife, PE – Brazil

Bruno Caramelli – Universidade de São Paulo (USP), São Paulo, SP – Brazil

Carisi A. Polanczyk – Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS – Brazil

Carlos Eduardo Rochitte – Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina (INCOR HCFMUSP), São Paulo, SP – Brazil

Carlos Eduardo Suaide Silva – Universidade de São Paulo (USP), São Paulo, SP – Brazil

Carlos Vicente Serrano Júnior – Instituto do Coração (InCor HCFMUSP), São Paulo, SP – Brazil

Celso Amodeo – Instituto Dante Pazzanese de Cardiologia/Fundação Adib Jatene (IDPC/FAJ), São Paulo, SP – Brazil

Charles Mady – Universidade de São Paulo (USP), São Paulo, SP – Brazil

Claudio Gil Soares de Araujo – Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ – Brazil

Cláudio Tinoco Mesquita – Universidade Federal Fluminense (UFF), Rio de Janeiro, RJ – Brazil

Cleonice Carvalho C. Mota – Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG – Brazil

Clerio Francisco de Azevedo Filho – Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, RJ – Brazil

Dalton Bertolim Précoma – Pontifícia Universidade Católica do Paraná (PUC/PR), Curitiba, PR – Brazil

Dário C. Sobral Filho – Universidade de Pernambuco (UPE), Recife, PE – Brazil

Décio Mion Junior – Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), São Paulo, SP – Brazil

Denilson Campos de Albuquerque – Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, RJ – Brazil

Djair Brindeiro Filho – Universidade Federal de Pernambuco (UFPE), Recife, PE – Brazil

Domingo M. Braile – Universidade Estadual de Campinas (UNICAMP), São Paulo, SP – Brazil

Edmar Atik – Hospital Sírio Libanês (HSL), São Paulo, SP – Brazil

Emilio Hideyuki Moriguchi – Universidade Federal do Rio Grande do Sul (UFRGS) Porto Alegre, RS – Brazil

Enio Buffolo – Universidade Federal de São Paulo (UNIFESP), São Paulo, SP – Brazil

Eulógio E. Martinez Filho – Instituto do Coração (InCor), São Paulo, SP – Brazil

Evandro Tinoco Mesquita – Universidade Federal Fluminense (UFF), Rio de Janeiro, RJ – Brazil

Expedito E. Ribeiro da Silva – Universidade de São Paulo (USP), São Paulo, SP – Brazil

Fábio Vilas Boas Pinto – Secretaria Estadual da Saúde da Bahia (SESAB), Salvador, BA – Brazil

Fernando Bacal – Universidade de São Paulo (USP), São Paulo, SP – Brazil

Flávio D. Fuchs – Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS – Brazil

Francisco Antonio Helfenstein Fonseca – Universidade Federal de São Paulo (UNIFESP), São Paulo, SP – Brazil

Gilson Soares Feitosa – Escola Bahiana de Medicina e Saúde Pública (EBMSP), Salvador, BA – Brazil

Glaucia Maria M. de Oliveira – Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ – Brazil

Hans Fernando R. Dohmann, AMIL – ASSIST. MEDICA INTERNACIONAL LTDA., Rio de Janeiro, RJ – Brazil

Humberto Villacorta Junior – Universidade Federal Fluminense (UFF), Rio de Janeiro, RJ – Brazil

Ines Lessa – Universidade Federal da Bahia (UFBA), Salvador, BA – Brazil

Iran Castro – Instituto de Cardiologia do Rio Grande do Sul (IC/FUC), Porto Alegre, RS – Brazil

Jarbas Jakson Dinkhuysen – Instituto Dante Pazzanese de Cardiologia/Fundação Adib Jatene (IDPC/FAJ), São Paulo, SP – Brazil

João Pimenta – Instituto de Assistência Médica ao Servidor Público Estadual (IAMSPE), São Paulo, SP – Brazil

Jorge Ilha Guimarães – Fundação Universitária de Cardiologia (IC FUC), Porto Alegre, RS – Brazil

José Antonio Franchini Ramires – Instituto do Coração Incor Hc Fmusp (INCOR), São Paulo, SP – Brazil

José Augusto Soares Barreto Filho – Universidade Federal de Sergipe, Aracaju, SE – Brazil

José Carlos Nicolau – Instituto do Coração (InCor), São Paulo, SP – Brazil

José Lázaro de Andrade – Hospital Sírio Libanês, São Paulo, SP – Brazil

José Péricles Esteves – Hospital Português, Salvador, BA – Brazil

Leonardo A. M. Zornoff – Faculdade de Medicina de Botucatu Universidade Estadual Paulista Júlio de Mesquita Filho (UNESP), Botucatu, SP – Brazil

Leopoldo Soares Piegas – Instituto Dante Pazzanese de Cardiologia/Fundação Adib Jatene (IDPC/FAJ) São Paulo, SP – Brazil

Lucia Campos Pellanda – Fundação Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), Porto Alegre, RS – Brazil

Luís Eduardo Paim Rohde – Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS – Brazil

Luís Cláudio Lemos Correia – Escola Bahiana de Medicina e Saúde Pública (EBMSP), Salvador, BA – Brazil

Luiz A. Machado César – Fundação Universidade Regional de Blumenau (FURB), Blumenau, SC – Brazil

Luiz Alberto Piva e Mattos – Instituto Dante Pazzanese de Cardiologia (IDPC), São Paulo, SP – Brazil

Marcia Melo Barbosa – Hospital Socor, Belo Horizonte, MG – Brazil

Marcus Vinícius Bolívar Malachias – Faculdade Ciências Médicas MG (FCMMG), Belo Horizonte, MG – Brazil

Maria da Consolação V. Moreira – Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG – Brazil

Mario S. S. de Azeredo Coutinho – Universidade Federal de Santa Catarina (UFSC), Florianópilis, SC – Brazil

Maurício Ibrahim Scanavacca – Universidade de São Paulo (USP), São Paulo, SP – Brazil

Max Grinberg – Instituto do Coração do Hcfmusp (INCOR), São Paulo, SP – Brazil

Michel Batlouni – Instituto Dante Pazzanese de Cardiologia (IDPC), São Paulo, SP – Brazil

Murilo Foppa – Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, RS – Brazil

Nadine O. Clausell – Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS – Brazil

Orlando Campos Filho – Universidade Federal de São Paulo (UNIFESP), São Paulo, SP – Brazil

Otávio Rizzi Coelho – Universidade Estadual de Campinas (UNICAMP), Campinas, SP – Brazil

Otoni Moreira Gomes – Universidade Federal de Minas Gerais (UFMG), Belo Horizonte, MG – Brazil

Paulo Andrade Lotufo – Universidade de São Paulo (USP), São Paulo, SP – Brazil

Paulo Cesar B. V. Jardim – Universidade Federal de Goiás (UFG), Brasília, DF – Brazil

Paulo J. F. Tucci – Universidade Federal de São Paulo (UNIFESP), São Paulo, SP – Brazil

Paulo R. A. Caramori – Pontifícia Universidade Católica do Rio Grande do Sul (PUCRS), Porto Alegre, RS – Brazil

Paulo Roberto B. Évora – Universidade de São Paulo (USP), São Paulo, SP – Brazil

Paulo Roberto S. Brofman – Instituto Carlos Chagas (FIOCRUZ/PR), Curitiba, PR – Brazil

Pedro A. Lemos – Hospital das Clínicas da Faculdade de Medicina da USP (HCFMUSP), São Paulo, SP – Brazil

Protásio Lemos da Luz – Instituto do Coração do Hcfmusp (INCOR), São Paulo, SP – Brazil

Reinaldo B. Bestetti – Universidade de Ribeirão Preto (UNAERP), Ribeirão Preto, SP – Brazil

Renato A. K. Kalil – Instituto de Cardiologia do Rio Grande do Sul (IC/FUC), Porto Alegre, RS – Brazil

Ricardo Stein – Universidade Federal do Rio Grande do Sul (UFRS), Porto Alegre, RS – Brazil

Salvador Rassi – Faculdade de Medicina da Universidade Federal de Goiás (FM/GO), Goiânia, GO – Brazil

Sandra da Silva Mattos – Real Hospital Português de Beneficência em Pernambuco, Recife, PE – Brazil

Sandra Fuchs – Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS – Brazil

Sergio Timerman – Hospital das Clínicas da Faculdade de Medicina da USP (INCOR HC FMUSP), São Paulo, SP – Brazil

Silvio Henrique Barberato – Cardioeco Centro de Diagnóstico Cardiovascular (CARDIOECO), Curitiba, PR – Brazil

Tales de Carvalho – Universidade do Estado de Santa Catarina (UDESC), Florianópolis, SC – Brazil

Vera D. Aiello – Instituto do Coração do Hospital das Clínicas da (FMUSP, INCOR), São Paulo, SP – Brazil

Walter José Gomes – Universidade Federal de São Paulo (UNIFESP), São Paulo, SP – Brazil

Weimar K. S. B. de Souza – Faculdade de Medicina da Universidade Federal de Goiás (FMUFG), Goiânia, GO – Brazil

William Azem Chalela – Instituto do Coração (INCOR HCFMUSP), São Paulo, SP – Brazil

Wilson Mathias Junior – Instituto do Coração (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), São Paulo, SP – Brazil

Exterior

Adelino F. Leite-Moreira – Universidade do Porto, Porto – Portugal

Alan Maisel – Long Island University, Nova York – USA

Aldo P. Maggioni – ANMCO Research Center, Florença – Italy

Ana Isabel Venâncio Oliveira Galrinho – Hospital Santa Marta, Lisboa – Portugal

Ana Maria Ferreira Neves Abreu – Hospital Santa Marta, Lisboa – Portugal

Ana Teresa Timóteo – Hospital Santa Marta, Lisboa – Portugal

Cândida Fonseca – Universidade Nova de Lisboa, Lisboa – Portugal

Fausto Pinto – Universidade de Lisboa, Lisboa – Portugal

Hugo Grancelli – Instituto de Cardiología del Hospital Español de Buenos Aires – Argentina

James de Lemos – Parkland Memorial Hospital, Texas – USA

João A. Lima, Johns – Johns Hopkins Hospital, Baltimore – USA

John G. F. Cleland – Imperial College London, Londres – England

Jorge Ferreira – Hospital de Santa Cruz, Carnaxide – Portugal

Manuel de Jesus Antunes – Centro Hospitalar de Coimbra, Coimbra – Portugal

Marco Alves da Costa – Centro Hospitalar de Coimbra, Coimbra – Portugal

Maria João Soares Vidigal Teixeira Ferreira – Universidade de Coimbra, Coimbra – Portugal

Maria Pilar Tornos – Hospital Quirónsalud Barcelona, Barcelona – Spain

Nuno Bettencourt – Universidade do Porto, Porto – Portugal

Pedro Brugada – Universiteit Brussel, Brussels – Belgium

Peter A. McCullough – Baylor Heart and Vascular Institute, Texas – USA

Peter Libby – Brigham and Women's Hospital, Boston – USA

Piero Anversa – University of Parma, Parma – Italy

Roberto José Palma dos Reis – Hospital Polido Valente, Lisboa – Portugal

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
Paulo Ricardo Avancini Caramori

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 114, Nº 4, April 2020

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
www.arquivosonline.com.br
SciELO: www.scielo.br

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

Graphic Design and Diagramming
SBC - Internal Design Department

Editorial Production
SBC - Internal Publication Department

The ads showed in this issue are of the sole responsibility of advertisers, as well as the concepts expressed in signed articles are of the sole responsibility of their authors and do not necessarily reflect the views of SBC.

This material is for exclusive distribution to the medical profession. The Brazilian Archives of Cardiology are not responsible for unauthorized access to its contents and that is not in agreement with the determination in compliance with the Collegiate Board Resolution (DRC) N. 96/08 of the National Sanitary Surveillance Agency (ANVISA), which updates the technical regulation on Drug Publicity, Advertising, Promotion and Information. According to Article 27 of the insignia, "the advertisement or publicity of prescription drugs should be restricted solely and exclusively to health professionals qualified to prescribe or dispense such products (...)".

To ensure universal access, the scientific content of the journal is still available for full and free access to all interested parties at:
www.arquivosonline.com.br.

Affiliated at the Brazilian Medical Association

SUPPORT

Ministério da **Educação**

Ministério da **Ciência e Tecnologia**

COVID-19 and the Heart

Tânia Mara Varejão Strabelli[1,2] *and David Everson Uip*[3,4,5]

Faculdade de Medicina Universidade de São Paulo,[1] *São Paulo, SP - Brazil*
Unidade de Controle de Infecção Hospitalar do Instituto do Coração (InCor HCFMUSP),[2] *São Paulo, SP – Brazil*
Centro Universitário Saúde ABC,[3] *Santo André, SP – Brazil*
Centro de Infectologia do Hospital Sírio-Libanês,[4] *São Paulo, SP – Brazil*
Centro de Contingência do Covid-19 do Estado de São Paulo,[5] *São Paulo, SP – Brazil*

We have been living with the new coronavirus pandemic since March 11, 2020. Initially, on January 1, 2020, the World Health Organization (WHO) declared the new coronavirus infection a global emergency and proceeded to name the disease COVID-19. The Coronavirus Study Group of the International Committee on Taxonomy of Viruses proposed the adoption of the name SARS-Cov-2.[1] Genomic sequencing and phylogenetic analysis have indicated that it is a betacoronavirus from the same subgenus as the severe acute respiratory syndrome (SARS) that caused an epidemic in China in 2003 and the Middle East respiratory syndrome (MERS) that caused the same condition in the Middle East in 2012. It has 96.2% genetic identity with betaCoV/bat/Yunnan, a virus isolated in bats. The structure of the virus's cell-binding receptor gene is very similar to that of the SARS coronavirus, and the virus appears to use the same angiotensive-converting enzyme 2 (ACE2) receptor to enter the cell.

The clinical picture of COVID-19 is similar to that of other respiratory viruses, namely, fever, generally dry cough, fatigue, and, in severer cases (5%), dyspnea, pulmonary bleeding, severe lymphopenia, and renal failure. Symptoms are mild in 80% of cases. Diagnosis of symptomatic cases should be confirmed by testing for the virus via polymerase chain reaction (PCR) of a nasal swab.

The cardiac complications of this disease have drawn physicians' attention. In a study evaluating 138 patients hospitalized for COVID-19, 16.7% developed arrhythmia, and 7.2% presented acute cardiac injury.[2] On the other hand, cardiologists at the San Raffaele Hospital in Milan, Italy, which is the referral hospital for cardiovascular complications from COVID-19, collected enzymes (BNP, troponin, CK-MB) from all patients to detect the prevalence of cardiac injury. As of March 9, of the 82 patients admitted, 19 of whom were in the intensive care unit, only one 43-year-old female patient had been admitted for chest pain with ST-segment changes and diagnosis of pneumonia. Her coronary angiography was normal.[3]

Keywords

Coronavirus-19/complications; betaCoV/bat/Yunnan/complications; Fever; Severe Acute Respiratory Syndrome; Dyspnea; Respiration Disorders; Risk Factors; Hypertension; Diabetes Mellitus.

Mailing Address: Tânia Mara Varejão Strabelli •
Av. Marechal Câmara, 160 sala 330. CEP 20020-907, Centro, RJ - Brazil
E-mail: tania.s@hc.fm.usp.br

DOI: https://doi.org/10.36660/abc.20200209

A large study published by the Chinese Center for Disease Control and Prevention, with data from 44,672 confirmed cases of COVID-19, reported a mortality of 2.3%. The most common comorbities in patients who died were arterial hypertension, diabetes mellitus, cardiovascular disease, and age over 70 years.[4]

Another published study[1] based on retrospective analysis of databanks from two hospitals in Wuhan (the Jin Yin-tan Hospital and the Tongji Hospital) evaluated 150 cases of laboratory confirmed infection with SARS-CoV-2, 68 (45%) of which resulted in death. The following discharge criteria were applied: no fever for at least 3 days, significant improvement in respiratory function, and 2 consecutive negative tests for the virus. There was a statistically significant difference for advanced age in patients who died ($p < 0.001$), but there was no difference between sexes ($p = 0.43$). A total of 63% (43/68) of patients who died had underlying diseases, in comparison with 41% (34/82) of patients who were discharged ($p = 0.0069$). Patients with associated cardiovascular disease had a greater risk of death ($p < 0.001$). There was also a higher incidence of secondary infections in patients who died compared to those who were discharged (16% [11/68] vs. 1% [1/82], $p = 0.0018$). Figure 1 shows higher values of inflammatory mediators in patients who died, and Figure 2 summarizes the causes of death.

Another study published in *The Lancet* [5] identified increased interleukin-6, high-sensitivity troponin I, and lactate dehydrogenase values as more frequent findings in hospitalized patients who died ($n = 54$) compared with those who survived ($n = 137$) in 2 hospitals in Wuhan, China. Of all the patients, 91 (48%) had some comorbidity, the following being the most common: arterial hypertension in 58 patients (30%), diabetes mellitus in 36 patients (19%), and chronic coronary disease in 15 patients (8%). However, in multivariate analysis of risk factors for outcome of death, only advanced age, higher Sequential Organ Failure Assessment (SOFA) score, and d-dimer greater than 1 μg/l at admission were statistically significant.

There is still no evidence that the use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) may affect the virus's activity. The Council on Hypertension of the European Society of Cardiology recommends that doctors and patients continue antihypertensive treatment as usual.

Another fundamental recommendation is that everyone is vaccinated against influenza, whose seasonal activity has already begun in Brazil, and which, to date, has higher mortality than COVID-19.

This is a time for vigilance, common sense, and scientific investigation. Medical societies must organize themselves in order to establish protocols for recognizing and treating complications.

Editorial

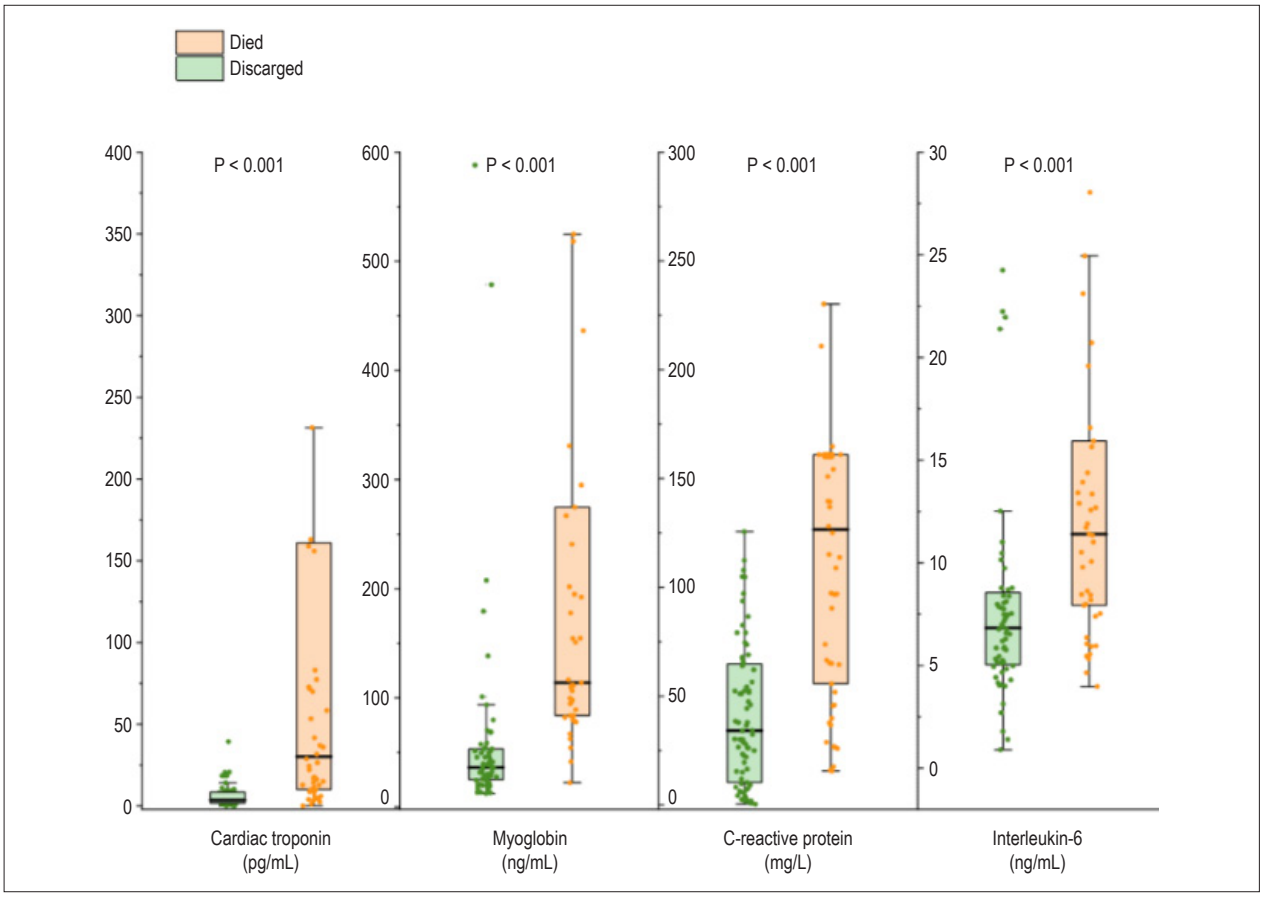


Figure 1 – *Main laboratory parameters in confirmed cases of COVID-19 by outcome.*[1]

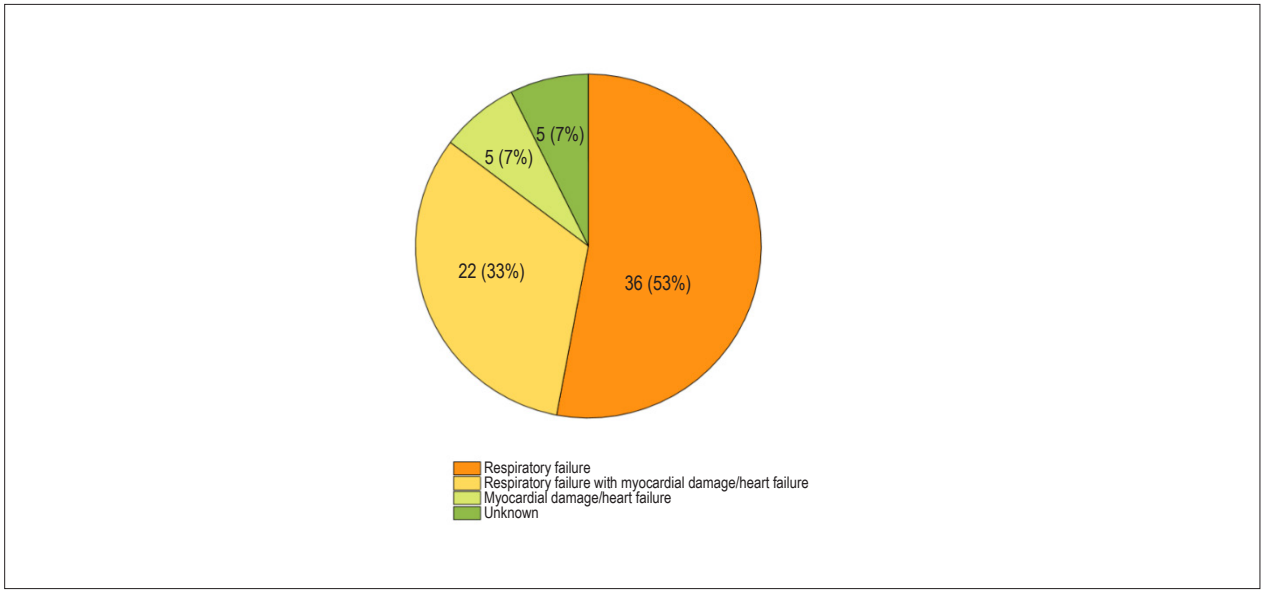


Figure 2 – *Summary of causes of death in 68 patients with confirmed COVID-19.*[1]

References

1. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Medicine, March,2020. https://doi.org/10.1007/s00134-020-05991-x
2. Wang D, Hu B, Hu C, Zhu F, Liu X,Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 Novel Coronovirus infected pneumonia in Wuhan, China. JAMA.2020,Feb 07. doi:10.1001/jama2020.1585.[Epub ahead of print]
3. www.tctmd.com/News/covid-19-and-heart-insights-front-lines. [Cited in 2020 March 17].Available from:www.tctmd.com
4. Centers for Disease Control and Prevention (CDC). The Novel Coronavirus Pneumonia Emergency Response Epidemiology Team. The epidemiological characteristics of an outbreak of 2019 novel coronavirus diseases (COVID-19)in China. Zhonghua Liu Xing Bing Xue Za Zhi. 2020;41(2):145-51. China, 202. China CDC Weekly.2020,2(8):113-122.
5. Zhou F, Yu T, Du R, Fan G,Liu Y,Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study.Lancet.2020 March 11. doi: https://doi.org/10.1016/50140-6736(20)30566-3.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Editorial

Physically Active Lifestyle as an Approach to Confronting COVID-19

Maycon Junior Ferreira,[1] Maria Cláudia Irigoyen,[2] Fernanda Consolim-Colombo,[2,3] José Francisco Kerr Saraiva,[4] Kátia De Angelis[1,3]

Laboratório de Fisiologia do Exercício - Departamento de Fisiologia - Universidade Federal de São Paulo (UNIFESP),[1] São Paulo, SP - Brazil
Instituto do Coração (InCor) - Faculdade de Medicina - Universidade de São Paulo,[2] São Paulo, SP - Brazil
Universidade Nove de Julho (UNINOVE),[3] São Paulo, SP - Brazil
Pontifícia Universidade Católica de Campinas (PUC-Campinas),[4] Campinas, SP - Brazil

The rapid, uncontrollable spread of the new coronavirus (SARS-CoV-2) throughout the world, in conjunction with its severity, led the Director-General of the World Health Organization (WHO) to characterize the situation as a pandemic on March 11, 2020.[1] It is currently possible to observe increasingly intense efforts on the part of health organizations and public authorities with the aim of containing the progress and spread of SARS-CoV-2. SARS-CoV-2 has emerged as a new subtype of human severe acute respiratory syndrome (SARS-CoV) characterized by high transmission capacity and induction of severe respiratory infection. Recent studies have demonstrated a high prevalence of hypertension and diabetes in elderly patients affected by COVID-19 who died in Wuhan, China,[2,3] which was the epicenter of the SARS-CoV-2 outbreak; this suggests that these comorbidities are important risk factors for deterioration and worse prognosis of complications associated with COVID-19.

Considering the recommendations for social isolation currently imposed in different countries, it is fundamental to encourage the population to maintain a physically active lifestyle routine as a preventative health measure during this period of confronting the spread of the virus. During periods of confinement at home, the population tends to adopt a sedentary routine, which favors increased body weight gain, as well as the emergence of comorbidities associated with greater cardiovascular risk, such as obesity, increased blood pressure, and glucose intolerance, in addition to psychosocial disorders such as anxiety and depression. Sedentary behavior, whether sitting, watching TV, or spending time in front of electronic devices, has in fact been associated with increased body weight in children, adolescents, adults and elderly[6] as well as with a marked increase in the risk of cardiovascular mortality.[7] It has, on the contrary, been shown that the risk of developing cardiovascular diseases and mortality is reduced in individuals with physically active life habits, such as going on moderately intense walks.[8] It has furthermore been demonstrated that the risk of upper respiratory tract infection due to coronavirus is potentially greater in the presence of immune system deficiency.[9] In this sense, there is strong evidence in the literature that practicing physical exercise is a beneficial measure for improving immunity.[10-12] The American College of Sports Medicine has recently published a guide suggesting that moderately intense physical activity should be maintained during the period of quarantine due to SARS-CoV-2, emphasizing the importance of every minute of physical activity to health.[13]

It is worth remembering that, for healthy and asymptomatic individuals, the WHO recommends at least 150 minutes of physical activity per week for adults and 300 minutes per week for children and adolescents.[14] This time of physical activity should be accumulated during the days of the week; it may be divided according to individual routine, and it should preferably be composed of it may be divided according to individual routine, and it should preferably be composed of moderate- and vigorous-intensity activity.. We emphasize the importance of advice from physical exercise professionals in order to adequately adapt practice of physical activities for the population. It is fundamental that individuals who regularly perform physical exercise maintain their practice, adapting them, however, to the current conditions of restricted movement. The importance of staying physically active should be even further emphasized for elderly individuals, who have been proven to present more comorbidities and greater cardiovascular risk, in addition to being more vulnerable to COVID-19. Populations with cardiovascular comorbidities should perform physical activities on a daily basis, maintaining pharmacological treatment and respecting their eventual physical limitations and the recommendations of healthcare professionals. Practice of physical exercise should be interrupted when symptoms related to COVID-19, such as fever, dry cough, and dyspnea, are present at rest.

It is important to emphasize that the home and family environment is also conducive to performing physical activity. In this manner, regardless of age range, the following behaviors and attitudes should be recommended, which will help the population stay physically active and maintain physical and mental health and which will be important for facing this moment of social isolation:

- Perform physical activities that are pleasurable, exploring spaces around the house and using equipment to move about;
- Perform daily activities, such as cleaning, maintaining, and organizing spaces around the house;
- Play and exercise with children, adolescents, and pets, using games that promote energy expenditure higher than resting;
- Avoid sedentary behavior, alternating time spent sitting or lying down with periods of physical activity, reducing time spent using electronic devices;

Keywords

Coronavirus-19; COVID-19; Exercise; Motor Activity; Sedentarism; Risk Factors; Prevention and Control.

Mailing Address: Kátia De Angelis •
Universidade Federal de São Paulo (UNIFESP), Edifício de Ciências Biomédicas, Departamento de Fisiologia (5º andar) - Rua Botucatu, 862. Postal Code 04023901, Vila Clementino, São Paulo, SP - Brazil
E-mail: prof.kangelis@yahoo.com.br

DOI: https://doi.org/10.36660/abc.20200235

- Set aside a few minutes for stretching, relaxation, and meditation activities.

In this manner, faced with the exponential growth of this pandemic in Brazil, healthcare professionals recommendations that the population maintain a physically active lifestyle should be understood as an important approach to fighting COVID-19 and the eventual consequences of social confinement, in conjunction with other measures that are being adopting by global public health sectors.

References

1. World Health Organization. (WHO) WHO Director-General's opening remarks at the media briefing on COVID-19. [Internet] [Cited in 2020 Mar22] Available from: https://www.who.int/dg/speeches/detail/who-director-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020.
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet.2020 Mar 11.pii:S0140-6736(20)30566-3
3. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020 Mar 13 [Epub ahead print]
4. Tanaka C, Reilly JJ, Tanaka M, Tanaka S. Changes in weight, sedentary behaviour and physical activity during the school year and summer vacation. Int J Environ Res Public Health. 2018 May 4 ;15(5)pii:E915.
5. Cureau F V, Sparrenberger K, Bloch K V, Ekelund U, Schaan BD. Associations of multiple unhealthy lifestyle behaviors with overweight/obesity and abdominal obesity among Brazilian adolescents: a country-wide survey. Nutr Metab Cardiovasc Dis. 2018;28(7):765–74.
6. Banks E, Jorm L, Rogers K, Clements M, Bauman A. Screen-time, obesity, ageing and disability: findings from 91266 participants in the 45 and up study. Public Health Nutr. 2011;14(1):34–43.
7. Patterson R, McNamara E, Tainio M, de Sá TH, Smith AD, Sharp SJ, et al. Sedentary behaviour and risk of all-cause, cardiovascular and cancer mortality, and incident type 2 diabetes: a systematic review and dose response meta-analysis. Eur J Epidemiol. 2018;33(9):811–29.
8. Hamer M, Chida Y. Walking and primary prevention: a meta-analysis of prospective cohort studies. Br J Sports Med. 2008;42(4):238–43.
9. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39(5):529–39.
10. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol. 2011;11(9):607-15.
11. Suzuki K. Chronic inflammation as an immunological abnormality and effectiveness of exercise. Biomolecules. 2019 Jun 7 ;9(6).pii: E223
12. Pedersen BK. Anti-inflammatory effects of exercise: role in diabetes and cardiovascular disease. Eur J Clin Invest. 2017;47(8):600–11.
13. American College of Sports. (ACSM). Staying active during the coronavirus pandemic. [Internet]. [Cited in 2020 Mar 16] Available from: https://www.exerciseismedicine.org/assets/page_documents/EIM_Rx%20for%20Health_%20Staying%20Active%20During%20Coronavirus%20Pandemic.pdf
14. World Health Organization. (WHO) . Global recommendations on physical activity for health. Geneva; 2010.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Analysis of >100,000 Cardiovascular Surgeries Performed at the Heart Institute and a New Era of Outcomes

Omar A.V. Mejia,[1] Luiz Augusto Ferreira Lisboa,[1] Luiz Fernando Caneo,[1] Elisandra Trevisan Arita,[1] Carlos Manuel de Almeida Brandão,[1] Ricardo Ribeiro Dias,[1] Roberto Costa,[1] Marcelo Biscegli Jatene,[1] Pablo Maria Alberto Pomerantzeff,[1] Luís Alberto Oliveira Dallan,[1] Fabio Biscegli Jatene[1]

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

Abstract

Background: The current challenge of cardiovascular surgery (CVS) is to improve the outcomes in increasingly severe patients. In this respect, continuous quality improvement (CQI) programs have had an impact on outcomes.

Objective: To assess the evolution of the incidence and mortality due to CVS, as well as the current outcomes of the Hospital das Clínicas Heart Institute of the University of São Paulo Medical School (InCor-HCFMUSP).

Methods: An outcome analysis of CVSs performed at the InCor, between January 1984 and June 2019. We observed the surgical volume and mortality rates in 5 time periods: 1st (1984-1989), 2nd (1990-1999), 3rd (2000-2007), 4th (2008-2015) and 5th (2016-2019). The CQI program was implemented between 2015 and 2016. The analysis included the total number of surgeries and the evolution of the most frequent procedures.

Results: A total of 105,599 CCVs were performed, with an annual mean of 2,964 procedures and mortality of 5,63%. When comparing the 4th and the 5th periods, the average global volume of surgeries was increased from 2,943 to 3,139 ($p = 0.368$), bypass graft (CABG), from 638 to 597 ($p = 0.214$), heart valve surgery, from 372 to 465 ($p = 0.201$), and congenital heart disease surgery, from 530 to 615 ($p = 0.125$). The average global mortality went from 7.8% to 5% ($p < 0.0001$); in CABG surgery, from 5.8% to 3.1% ($p < 0.0001$); in heart valve surgery, from 14% to 7.5% ($p < 0.0001$) and in congenital heart disease surgery, from 12.1% to 9.6% ($p < 0.0001$).

Conclusion: In spite of a recent trend towards increased surgical volume, there was a significant decrease in operative mortality in the groups studied. After the implementation of the CQI program, the mortality rates were closer to international standards. (Arq Bras Cardiol. 2020; 114(4):603-612)

Keywords: Cardiovascular Surgical Procedures/trends; Quality Improvement; Patient Safety; Hospital Mortality; Database.

Introduction

Cardiovascular surgery has undergone transformations throughout its history, especially after the consolidation of large databases.[1] These data helped reduce surgical mortality by implementing data-oriented improvements.[2] At that time, this was the reality of only a few centers in the world.

In 1984, the Hospital das Clínicas Heart Institute of the University of São Paulo Medical School (InCor-HCFMUSP) database was structured wih the purpose of defining and improving cardiovascular surgery outcomes. Thus, the InCor, one of the largest Cardiology centers in Brazil, took its first step into the virtuous cycle of outcome continuous improvement.

In this respect, a national analysis of cardiovascular surgery outcomes already showed a mortality of 8%,[3] virtually twice as much than that in the best centers worldwide, although the data were obtained from an administrative database. There was a wide range of justifications, such as healthcare access difficulties, lack of adherence to protocols and socioeconomic conditions. In fact, it was quite difficult to identify the health service weaknesses, given the lack of clinical data available.

In InCor, limitations in variable definitions, regarding both data completeness and consistency, as well as the lack of reference parameters to follow the results caused the development of a data-driven culture over time, which was strengthened after the implementation and validation of the EuroSCORE I and the modified Parsonnet's score.[4] Afterwards, the InCor created the InsCor, becoming one of the few centers in the world to have its own risk model for prediction, planning and optimization of outcomes.[5]

Over time, the InCor took the lead by establishing a partnership with the São Paulo State Department of Health, in order to build the Sao Paulo Registry of Cardiovascular Surgery (REPLICCAR).[6] Next, the InCor established the Patient Safety and Quality Surgical Unit, which gave rise to the CQI Program, consolidated in 2016, whose initial mission was to reduce mortality rates in cardiovascular surgery.

Mailing Address: Omar A.V. Mejia •
Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo – Av. Doutor Enéas de Carvalho Aguiar, 44. Postal Code 05403-900, São Paulo, SP – Brazil
E-mail: omar.mejia@incor.usp.br
Manuscript received October 24, 2019, Manuscript revised October 24, 2019, accepted November 26, 2019

DOI: https://doi.org/10.36660/abc.20190736

The purpose of this study is to assess the evolution of the incidence and and mortality of cardiovascular surgery, as well as the influence of the CQI Program in one of the centers of reference in cardiology in Brazil: the InCor-HCFMUSP.

Methods

Sample

An observational retrospective study from InCor database. We collected information on the surgical volume and mortality outcomes from January 1984 to June 2019. To facilitate this analysis, data were grouped into 5 periods: 1984-1989; 1990-1999; 2000-2007; 2008-2015 and 2016-2019. Thus, we analysed the surgical volume and mortality rates in general, as well as those related to the groups with the highest surgical volume and mortality rates (Coronary, Valvular, Congenital and Arrhythmias). In addition, the evolution of mortality rates in the last two periods (4th and 5th) for Aortic Valve Surgery, Mitral Valve Surgery, Aortic Valve Surgery + Mitral Valve Surgery, CABG + Valve Surgery (Aortic or Mitral) and Aortic Dissection Surgery was analysed in isolation.

Data collection, definition and organization

The InCor database (SI3)[7] includes clinical and follow-up data of patients inside and outside the hospital. Filling out this register is compulsory and performed by employees from several healthcare areas. The data are placed online (http://si3/) with a personal password and user. Data completeness and veracity were validated by the Incor Hospital Medical Information Unit, by the Assistance Operations Management and by the Patient Safety and Quality Surgical Unit. Data of the first publication, "Evolution of Cardiovascular Surgery at the Instituto do Coracao: Analysis of 71,305 Surgeries", were retrieved and analysed together.[8] Surgical mortality was defined as any death occurring within 30 days after the main procedure, in or out of the hospital.

Inclusion Criteria

All cardiovascular procedures performed at the InCor, between January 1984 and July 2019.

Exclusion Criteria

For the analysis by procedure type, emergency or rescue procedures were excluded.

The CQI Program

Envisioning a new era of cardiovascular surgical outcomes, the new InCor management, led by Prof. Fábio Jatene, created, inside the Cardiovascular Surgery Division of Incor, the Patient Safety and Quality Surgical Unit (UCQSP). This unit aims at supporting the construction of a safety culture, by promoting transparency, standardizing training courses, improving staff work and monitoring performance. In order to converge these and other activities, the UCQSP established the CQI Program in Cardiovascular Surgery.[9] To this end, an alignment with the Information Technology Service and the Hospital Medical Information Unit of the InCor was crucial to monitor the program implementation. Thus, the initial set of measures of the CQI Program was:

1) establish annual goals of surgical volume and outcomes;
2) public and monthly presentations of the outcomes;
3) implementation of a surgical Checklist and its propagation to 100% of the surgical procedures;
4) establishment of a clinical/surgical outpatient setting for all groups;
5) monitoring of adherence to the perioperative protocols established;
6) multidisciplinary approaches to all surgeries and/or patients at high risk;
7) assessment of the cause of operative mortality using the POCMA (Phase of Care Mortality Analysis) process;
8) requirement of quality improvement metrics for each area involved in healthcare;
9) development of Researches in Quality and Safety;
10) accurate indication and timing of surgery for urgency/emergency patients.

Statistical analysis

Regarding the mortality rates observed, the periods were compared using a two-tailed test for comparison of proportions. In 2019, it was observed that the second and the first semester had the same number of surgeries and average deaths. From 1984 to 2007, for the Arrhythmia group, only the annual mean of the number of surgeries perfomed in each period was available. Therefore, we considered that the number of surgeries carried out in each year was equal to the average of the period, in order to estimate the p-value. For the variable number of surgeries, the two-tailed Mann-Whitney test was used. The level of significance established was 0.05. The R software (version 3.5.3) was used for the analyses and graphs. The Excel software was used to consolidate the original basis.

Ethics and consent term

This Project was carried in the UCQSP, with the approval of the hospital management, as a study on quality improvement. It was a database study with no identification of patients. Therefore, the Free and Informed Consent Form was not required.

Results

A total of 105,599 CVSs were performed, with an annual mean of 2,964 procedures and mortality of 5.63%.

In the total volume analysis, there was an increase of 32.5% between the 1st and 2nd periods ($p = 0.001$) and of 35.3%, between the 2nd and 3rd periods ($p = 0.0001$). There was a decrease of 22.7% between the 3rd and 4th periods ($p = 0.0006$) and a slight increase of 6.7% between the 4th and 5th periods ($p = 0.3677$).

In relation to CABG surgery, there was an increase of 18.3% between the 1st and 2nd periods ($p = 0.0145$), and of 9.2%, between the 2nd and 3rd periods ($p = 0.0293$).

There was a decrease of 42.3% between the 3rd and 4th periods (p = 0.0002), and of 6.4%, between the 4th and 5th periods (p = 0.2141).

In valve surgeries, there was an increase of 8.5% between the 1st and 2nd periods (p = 0.1471), and of 37.6%, between the 2nd and 3rd periods (p = 0.0001). This increment decreased in the same proportion between the 3rd and 4th periods (p = 0.0009). However, there was an increase of 24.9% between the 4th and 5th periods (p = 0.2019).

In congenital surgeries, there was an increment of 23.4% between the 1st and 2nd periods (p = 0.0020), and of 37.8%, between the 2nd and 3rd periods (p = 0.0077). There was a decrease of 22.7% between the 3rd and 4th periods (p = 0.0312), and an increase of 16.1%, between the 4th and 5th periods (p = 0.1250).

In arrhythmia surgeries, there was an increase of 154.6% between the 1st and 2nd periods (p = 0.0001), 68% between the 2nd and 3rd periods (p = 0.0001), 12.6% between the 3rd and 4th periods (p = 0.0084), and of 1.6% between the 4th and 5th periods (p = 0.8081) (Table 1).

In the total mortality analysis, although there was a decrease in mortality of 1% between the 1st and 2nd periods (p = 0.0001), there was an increase of 0.1% between the 2nd and 3rd periods (p = 0.5227), and of 2.9% between the 3rd and 4th periods (p = 0.0001). However, there was a decrease of 2.8% between the 4th and 5th periods (p = 0.0001), which resulted in a decrease of 0.8% between the 1st and 5th periods (0.0051).

In relation to CABG surgery, there was a decrease in mortality of 0.1% between the 1st and 2nd periods (p = 0.7088), with an increase of 0.5% between the 2nd and 3rd periods (p = 0.1072), and of 1% between the 3rd and 4th periods (p = 0.0121). Nonetheless, there was a decrease of 2.6% between the 4th and 5th periods (p = 0.0001), achieving a decrease of 1.3% between the 1st and 5th periods (p = 0.0092).

In valve heart surgeries, there was an increase in mortality of 0.3% between the 1st and 2nd periods (p = 0.6693), of 0.5% between the 2nd and 3rd periods (p = 0.4174), and of 5.5% between the 3rd and 4th periods (p = 0.0001). However, there was a decrease of 6.5% between the 4th and 5th periods (p = 0.0001), ending up with a decrease of 0.2% between the 1st and 5th periods (p = 0.8946).

In congenial surgeries, there was a decrease in mortality of 0.9% between the 1st and 2nd periods (p = 0.1993), and of 2.7% between the 2nd and 3rd periods (p = 0.0001). Although there was an increase in mortality of 6.9% between the 3rd and 4th periods (p = 0.0001), there was a decrease of 2.5% between the 4th and 5th periods (p = 0.0017). When we compared the 1st and 5th periods, there was an increase in mortality of 0.7% (p = 0.3943).

In arrhythmia surgeries, there was a decrease in mortality of 1.2% between the 4th and 5th periods (p = 0.0001). We could not accurately retrieve the data on mortality of the arrhythmia surgeries performed in the 1st, 2nd and 3rd periods. (Table 2)

The graphs of global, coronary, valve, and congenital volume and mortality in > 35 years of the InCor are shown in Figures 1, 2, 3 and 4, respectively.

Additionally, we provided the annual volume (Table 3) and mortality (Figure 5) rates of the most complex and most frequently perfomed procedures in cardiovascular surgery since 2008: Acute Aortic Dissection, Congenital, Isolated CABG, CABG + Valve, Aortic Valve, Mitral Valve, and Aortic Valve + Mitral Valve.

For didactic purposes, we decided to compare these procedures in the 4th and 5th periods as well. Therefore, in Acute Aortic Dissection, the average annual volume increased 66% (p = 0.1060) and mortality decreased 11.2% (p=0.0016). In CABG + Valve, the average annual volume decreased 22.4% (p = 0.1481) and mortality reduced 12.1% (p = 0.0001). In Mitral Valve surgery, the average annual volume increased 34.1% (p = 0.1535) and mortality reduced 6.4% (p < 0.0001). In Aortic Valve surgery, the average annual volume increased 14.6% (p = 0.1481) and mortality reduced 6.7% (p < 0.0001). In Mitral Valve surgery + Aortic valve, the average annual volume increased 22% (p = 0.2688) and mortality reduced 11.9% (p < 0.0001) (Figure 5).

We also analysed two procedures considered the state of the art in cardiovascular surgery: Off-pump CABG surgery (OPCAB) and Valve Repair, for periods 4 and 5. The annual average volume of OPCAB decreased 49.8% (p = 0.0040) and mortality increased 0.8% (p = 0.7018). Still, the annual average volume of Valve Repairs reduced 5.7% (p = 0.8081), but mortality reduced 3.8% (p = 0.0427).

Discussion

We carried out a time series analysis of the volume and mortality in cardiovascular surgeries in > 35 of the InCor, one of the greatest intitutions in Latin America which, in 2016, established its CQI Program. These information were obtained

Table 1 – Number of Procedures per Surgical Group at the InCor during the 5 periods

	Period 1	Period 2	Period 3	Period 4	Period 5
Total	2,122	2,812	3,806	2,943	3,139
Groups Selected					
Coronary	856	1,013	1,106	638	597
Valve	400	434	597	372	465
Congenital	403	497	685	530	615
Arrhythmias	238	606	1,018	1,146	1,165

Table 2 – Mortality Rates per Surgical Group of the InCor during the 5 periods

	Period 1	Period 2	Period 3	Period 4	Period 5
Total	5.79%	4.75%	4.86%	7.78%	4.99%
Groups Selected					
Coronary	4.44%	4.29%	4.79%	5.78%	3.14%
Valve	7.63%	7.95%	8.44%	13.96%	7.47%
Congenital	8.85%	7.94%	5.27%	12.13%	9.60%
Arrhythmias				2.15%	0.94%

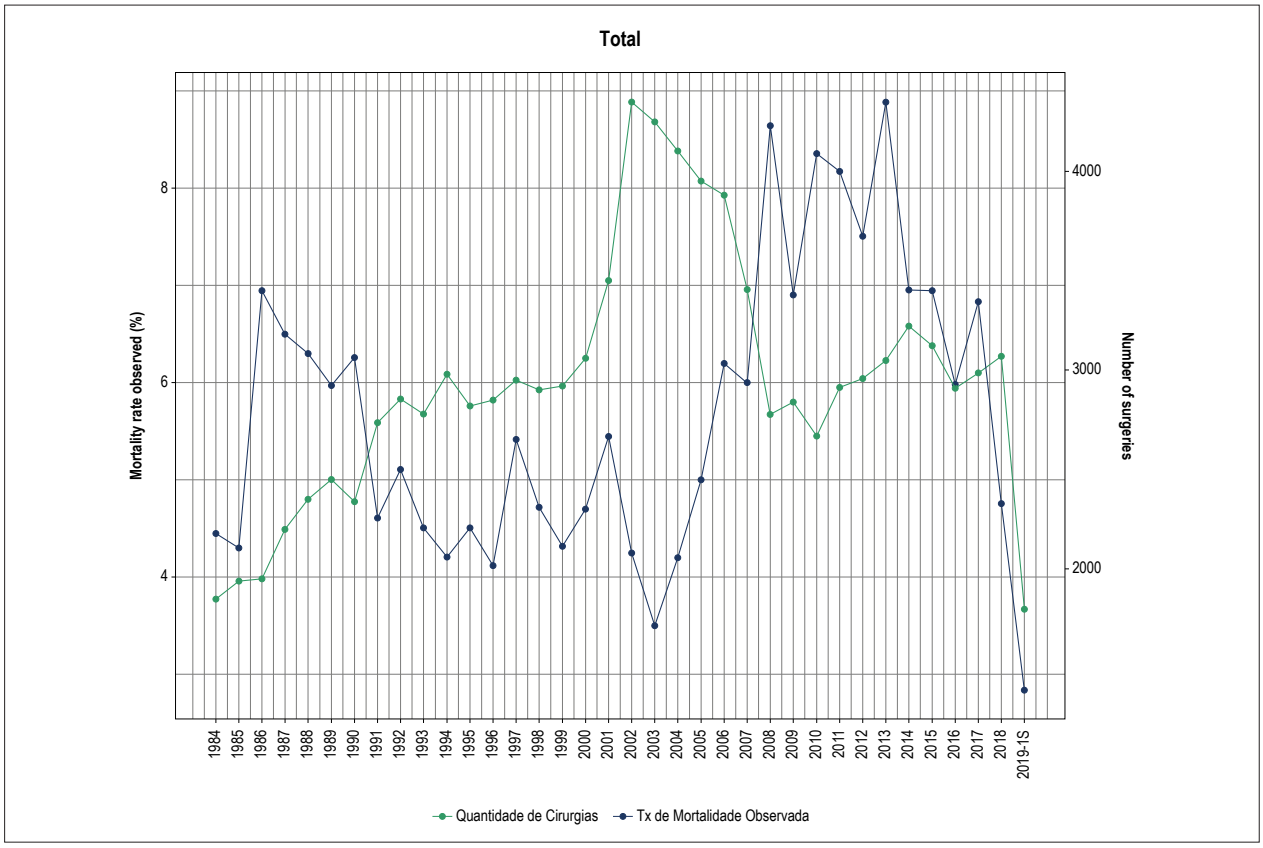


Figure 1 – *Year-by-year graph of global surgical volume and mortality in > 35 years of the InCor.*

from the InCor database, which was founded in 1984, at the same time that the New York State database was established.[10] This is also the period when a series of risk scores began to arise all over the world, with the purpose of stratifying patients, adjusting risk and monitoring the outcomes.[11]

These initiatives came at a time when patients had more comorbid conditions and, at the same time, the most complex surgeries were influenced by the increase in life expectancy.[12] It was the ideal scenario to start measuring the outcomes and optimizing the strategies. Perhaps one of the highest impact projects on outcomes continuous improvement has been the creation of the EuroSCORE[13] and the STS score[14] which, through the estimation of expected mortality, allowed us to plan, prepare and even look for new treatment alternatives for the patients. The adoption of these instruments in surgical practice enabled the phenomenon to develop. While the centers started to make their measurements, the outcomes observed continued to improve to the extent that the scores had to be recalibrated in order to survive.[15]

At the InCor, the measurements started to be taken in 2007 with the incorporation of the EuroSCORE and the 2000 Bernstein-Parsonnet model, for estimation of expected mortality.[4] These models, which were validated first, were used by the INCOR to elaborate its own model: the InsCor.[5] In the evolution of outcomes, this corresponds to period 4 of the present analysis. It was in this period that the culture of data and outcomes measurements began to consolidate, although a decrease in the surgical volume at the InCor, both in general surgery and in the subgroup ones, resulted in a proportional increase in surgical mortality rates. In addition,

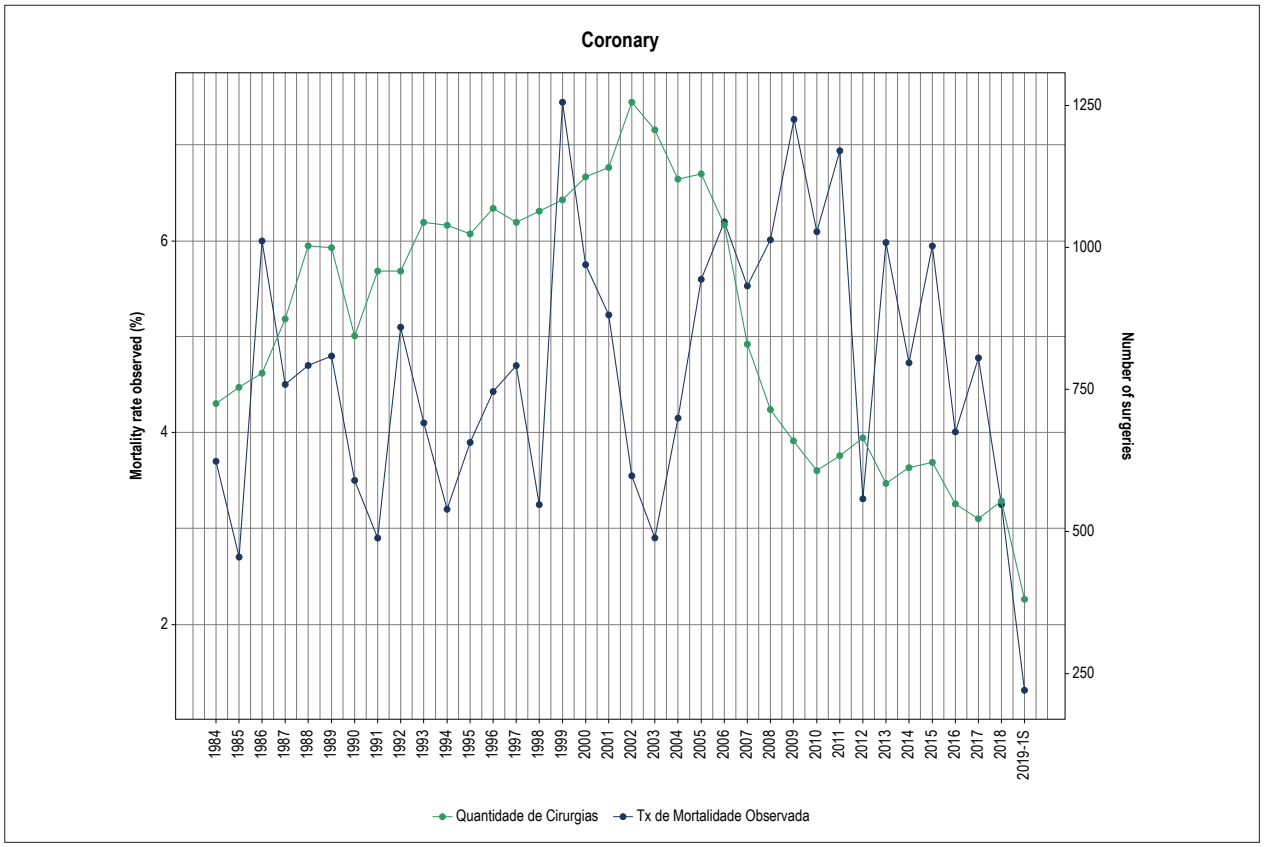


Figure 2 – *Year-by-year graph of volume and mortalidade in CABG surgery in > 35 years of the InCor.*

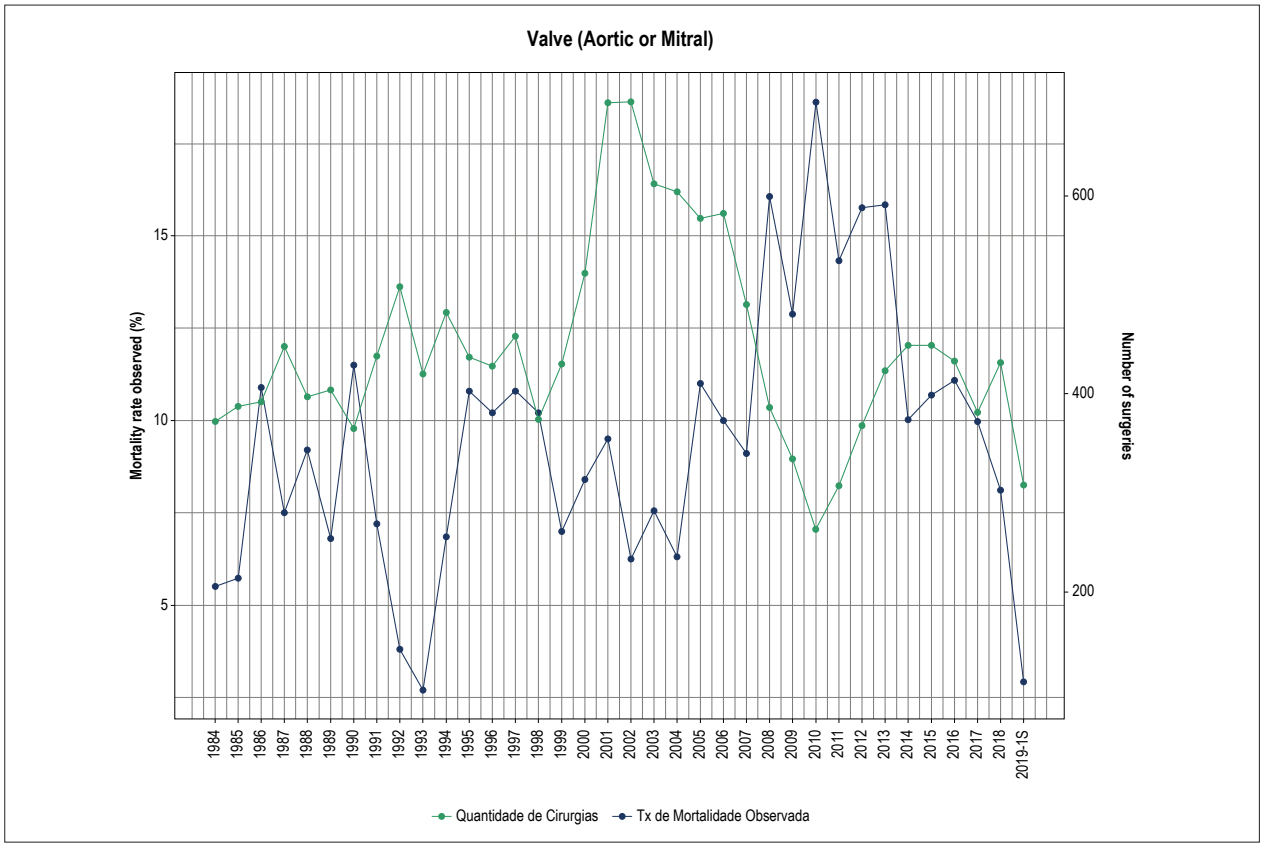


Figure 3 – *Year-by-year graph of volume and mortalidade in Valve Cardiac Surgery in > 35 years of the InCor.*

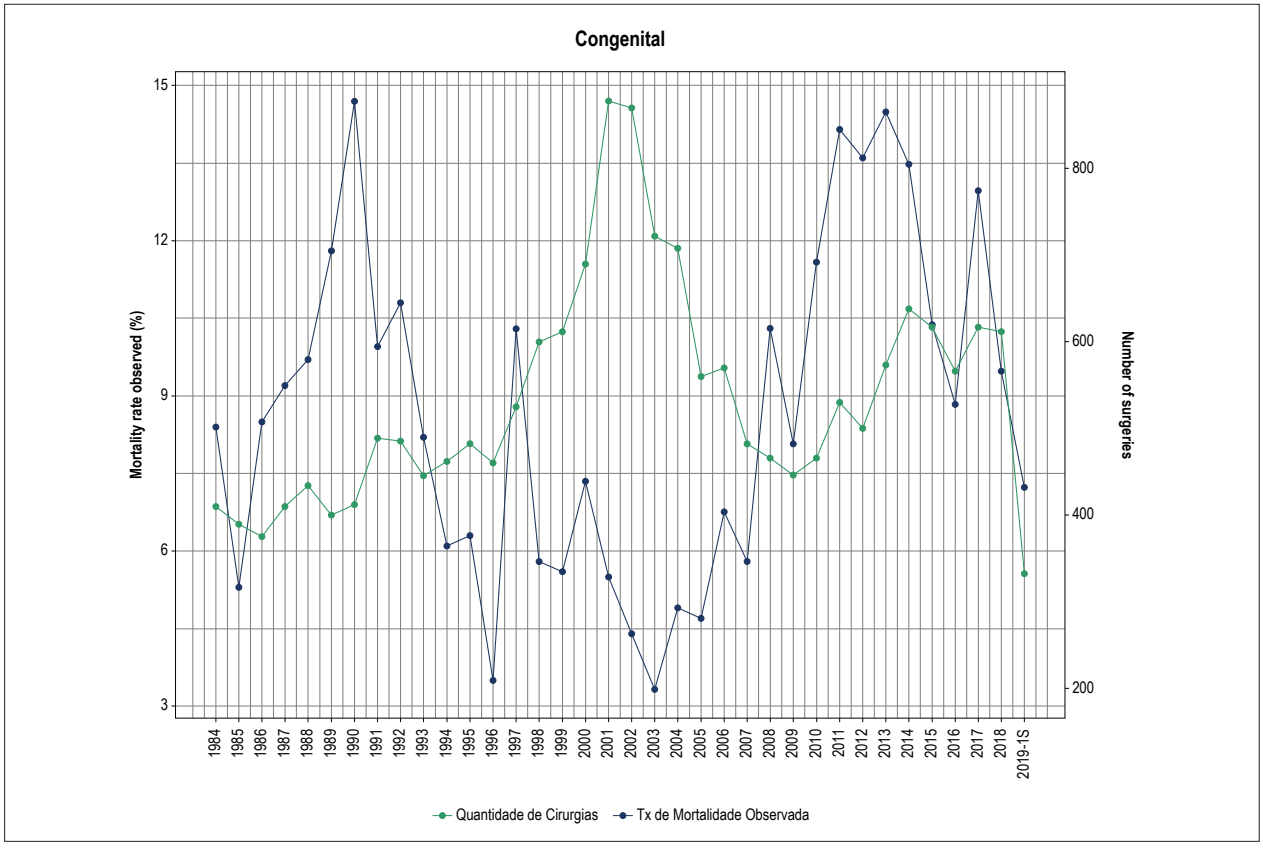


Figure 4 – *Year-by-year graph of volume and mortality in Congenital Heart Disease Surgeries in > 35 years of the InCor.*

Table 3 – Annual volume categorized by Procedure type (2008 – 1S/2019)

	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	1S 2019
Acute Aortic Dissection	42	36	54	25	19	40	78	77	72	76	72	44
Congenital	466	446	466	530	500	573	638	617	566	617	612	332
CABG	715	660	607	634	665	583	611	622	547	523	554	381
CABG + Valve	76	68	65	68	79	88	89	62	40	67	46	39
Aortic Valve	176	153	138	153	164	211	215	191	198	173	214	109
Aortic and Mitral Valve	68	59	49	66	54	49	51	63	55	58	67	50
Mitral Valve	210	181	125	154	204	212	234	258	235	208	217	199

although in this period there was the implementation of certain improvement initiatives, these were not convergent, and, consequenlty, could not be structured and far less sustainable.

The success of centers that had already started to work on the organization and structuring of improvement programs started to show results. In this respect, in 2012, the European Association for Cardio-Thoracic Surgery (EACTS) established its Quality Improvement Programme (QUIP) with the purpose of improving the outcomes, as well as integrating strategies for quality improvement.[16]

The Cardiovascular Surgery Division of the InCor started to create improvement initiatives through an organizational culture that focused on reducing mortality outcomes by following established goals. These goals at first followed historical data, which means improving one's own results. This is one of the best ways to create progressive and sustainable results. Because it understood the importance of multicenter registries and of continuous and collaborative learning, the InCor, by means of a partnership with the SES-SP, and the FAPESP, created, in 2013, the Paulista Cardiovascular Surgery Registry.[6] After this initiative, the InCor gained a better understanding of the outcomes and could guide its strategies better. As a result, in 2016, the InCor, with the establishment of a data-driven culture, converged its improvement measures through the implementation of its CQI Program.[9]

This analysis was carried out with 105,599 cardiovascular surgeries and it is possible to observe that, since 1984, the

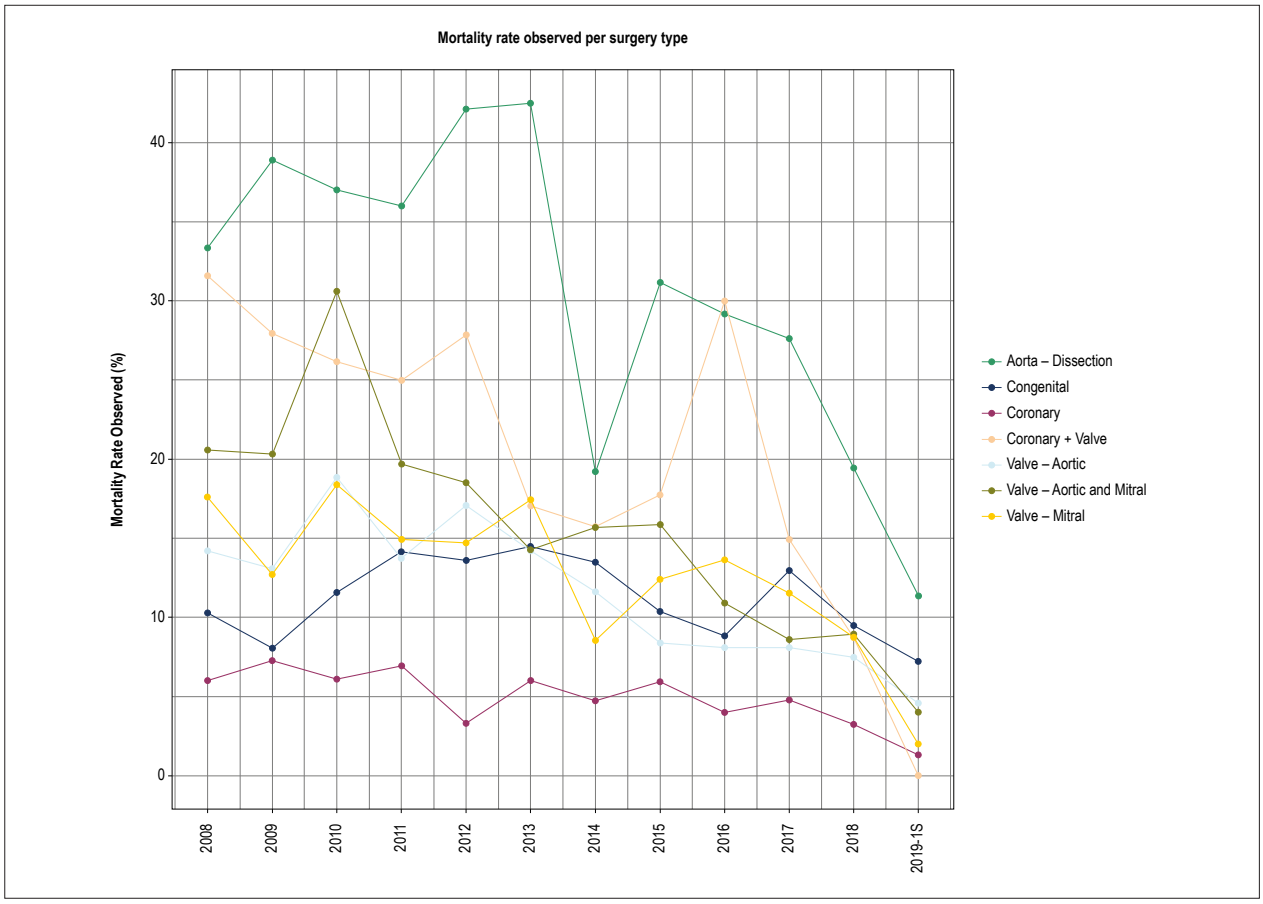


Figure 5 – *Year-by-year graph of the volume and mortality of the most complex and most frequently performed procedures in cardiovascular surgery since 2008.*

annual surgical volume has only increased, with the largest increase occurring in the 3rd period. The annual death rate was progressively increasing until the 4th period. The significant growth in surgical volume between the 2nd and 3rd periods (35%) caused the increase in mortality rate to be insignificant (0.1%). Nevertheless, the major decrease in surgical volume in the 4th period (22.7%) caused the mortality rate to increase significantly (2.9%). Although surgical volume growth between the 4th and 5th periods (6.7%) was not significant, the mortality rate reduced significantly (2.8%). Anyway, since its origins until the current period of the InCor, there has been a significant increase in surgical volume (47.9%), with a decrease in mortality rates (0.8%).

The significant decrease in the global surgical volume in period 4 was directly related with the significant decrease in surgical volume in all subgroups, excepted for the arrhythmia subgroup. This was more evident in the CABG group, most probably due to the boom in percutaneous procedures, such as coronary angioplasty.[17] Moreover, new evidence changed the practice of cardiovascular disease treatment, with the advances in drug therapy[18] and accurate indication for surgical intervention.[19] Here, we highlight the role of Science in balancing and adjusting the scenario for the benefit of better patient outcomes.

The decreased volume of CABG was significant between the 3rd and 4th periods (42.3%). However, we can say that it stopped to decline, since between the 4th and 5th periods, there was a decrease of only 6.4% ($p = 0.21$). We can see that, even though the highest CABG volume occurred in the 3rd period, the mortality rate has also increased (0.5%). Although this was not significant, it shows an increase in the number of deaths in this period. As described before, the incorporation of risk scores into our practice only took place by the beginning of the 4th period, which may explain to some extent the outcomes observed. As a result, the reduction of 42.3% in CABG volume in the 4th period undoubtedly impacted the mortality rate, which reached 5.78% ($p = 0.01$). What is evident is that, even though the volume reduction was not significant, in the 5th period, the mortality rate reduced 2.6% ($p = 0.0001$). By examining Figure 2, we note that the mortality rate in CABG surgeries reached 1% in 2019, a historic achievement, which is very close to the results of the best centers in the world.[20]

The volume of Valve Surgeries, which had been progressively increasing, suffered a significant reduction in the 4th period (37.6%), with a significant increase in mortality (5.5%). However, in the 5th period, the surgical volume increased 24.9% ($p = 0.20$), and there was a decrease of 6.5% in the

mortality rate (p = 0.0001). As the statistical data show, this is not only explained by the volume increase, but rather by the continuous outcome improvements, which reached, in 2019, a mortality of 2% in mitral valve surgery and of 5% in aortic valve surgery. The latter should continue to decline due to increased referral of more severe cases to transcatheter aortic valve implantation (TAVI).

In the congenital surgery group, there was also a significant surgical volume reduction in the 4th period (22.7%), which may have influenced the significant increase in mortality (6.9%). However, even with a modest volume increase in the 5th period (16.1%), mortality reduced significantly (2.5%). This also reflects the continuous implementation of improvement measures by the staff and the cardiovascular surgery division which, by 2019, has already reduced mortality rates to 7% (Figure 4).

For arrhythmia surgery, the 5th period was quite satisfactory because, in addition to a significant volume increase (389.5%), there was a reduction in mortality of 1.2% (p = 0.0001).

On the other hand, in relation to the isolated procedures, which have been presenting an expressive increase since 2008, we compared the 4th and 5th periods. We observed that the cases of Acute Aortic Dissection Surgeries increased 66% (p = 0.1060), and mortality reduced 11.2% (p = 0.0016). In 2019, the results already reach 11% for a mean mortality in the best centers of >20%.[21] It is important to mention that several protocols were structured taking into account the best moment for the surgical approach and the standardization of the surgical technique. In CABG + Valve surgeries, the average annual volume had a modest reduction of 22.4% (p = 0.1481). However, there was a significant mortality reduction (12.1%). In 2018, the mortality rate was 8% and, in 2019, we still have not registered any deaths due to this associated procedure. In mitral valve surgery, the average annual volume increased 34.1% (p = 0.1535), with a reduction in mortality of 6.4% (p < 0.0001). Until the first period of 2019, mortality had already reached 2%. In aortic valve surgery, the mean annual volume increased 14.6% (p = 0.1481) and there was also a significant decrease in mortality (6.7%). In 2019, mortality also followed a downward trend and is already at 5%. In the combined mitral and aortic valve repairs, the average annual volume increased 22% (p = 0.2688) and mortality reduced 11.9% (p < 0.0001). The positive mortality outcomes of the valve group is also the result of strong efforts towards the establishment of a line of care, of a multidisciplinary outpatient surgery clinic and the standardization of surgical techniques. Besides, this is a population at high risk, with 56% of rheumatic disease patients, 75% of patients in functional classes III and IV and 31% of reoperations.[22]

The purpose of this analysis is to show the evolution of cardiovascular surgery in one of the centers with the greatest operative volume in South America, where > 80%[23] of the patients are assisted under Brazil's Unified Health System (SUS), which makes it a reference hospital that receives all types of patient referrals for different procedures. Unquestionably, the decrease in surgical volume in the 4th period had an impact on mortality in a context that still focused on surgical volume, because evidence shows that the improvement in mortality outcomes due to volume were replaced by improvements resuting from the CQI programs,[24,25] including at university hospitals, which would be our case,[26] and in several parts of the world.[27,28]

Within the package of measures developed by the InCor through its CQI program, previously mentioned, it is worth to highlight the implementation of the InCor Checklist. This project was initiated in 2014, but it was only after 2016 that it became compulsory for all surgeries. Research projects in the area of Quality and Safety have favoured partnerships financed by the FAPESP, such as the cooperation with the Fuwai Hospital, in China, and the partnership of the REPLICCAR II with the Harvard University Department of Public Health (www.repliccar.com.br).

Undoubtedly, the greatest challenge should be sustainability and, above all, the continuous outcomes improvement. To this end, strategies that aim at reducing morbidity, optimizing processes to reduce hospital stay time and that focus on improving patient experience are required. Programs like this could be spread in Brazil, focusing on standardization and continuous structuring of good quality practices, regardless of the surgical volume.

Limitations

We note 3 limitations: 1) This is a unicentric and retrospective study, which would hinder the generalization of our conclusions. However, the large surgical volume and the existence of an institutional registry that improves over time help minimize this bias. 2) The lack of patient stratification based on risk makes it difficult to understand whether the decrease in surgical mortality would be more associated with a greater proportion of patients at low risk. A subanalysis of more recent periods (from 2013 to 2019) was carried out and we found a significant decrease in mortality with no differences in the surgical volume or in the risk estimated by the EuroSCORE II. 3) The CQI program was consolidated in 2016, but improvement measures date back to 2007. In fact, isolated actions can be traced back to 2007, but the formulation and structuring of the CQI program were established between 2015 and 2016. In practice, we can say that the package of measures converged in 2016, which may explain the mortality reduction in all groups.

Conclusions

In spite of a recent trend towards increased surgical volumes, except for CABG surgery, a significant decrease in the general surgical mortality rate and in the groups studied was evident. The consolidation of the CQI program at the InCor has been associated with the progressive decrease in surgical mortality, which corroborates the evidences, regardless of the scenario or region. After the consolidation of the CQI program, the mortality rates were close to international standards.

Author contributions

Conception and design of the research: Mejia OAV, Lisboa LAF, Jatene FB; Acquisition of data: Mejia OAV, Lisboa LAF,

Arita ET; Analysis and interpretation of the data: Mejia OAV, Lisboa LAF, Caneo LF, Brandão CMA, Dias RR, Costa R, Jatene MB, Pomerantzeff PMA, Jatene FB; Statistical analysis and Writing of the manuscript: Mejia OAV; Critical revision of the manuscript for intellectual content: Lisboa LAF, Caneo LF, Arita ET, Brandão CMA, Dias RR, Costa R, Jatene MB, Pomerantzeff PMA, Jatene FB.

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. D'Agostino RS, Jacobs JP, Badhwar V, Fernandez FG, Paone G, Wormuth DW, et al. The Society of Thoracic Surgeons Adult Cardiac Surgery Database: 2019 Update on Outcomes and Quality. Ann Thorac Surg. 2019;107(1):24-32.
2. Grover FL, Shroyer AL, Hammermeister K, Edwards FH, Ferguson TB Jr, Dziuban SW Jr, et al. A decade's experience with quality improvement in cardiac surgery using the Veterans Affairs and Society of Thoracic Surgeons national databases. Ann Surg. 2001;234(4):464-74.
3. Ribeiro AL, Gagliardi SP, Nogueira JL, Silveira LM, Colosimo EA, Lopes do Nascimento CA. Mortality related to cardiac surgery in Brazil, 2000-2003. J Thorac Cardiovasc Surg. 2006;131(4):907-9.
4. Mejía OA, Lisboa LA, Dallan LA, Pomerantzeff PM, Moreira LF, Jatene FB, et al. Validation of the 2000 Bernstein-Parsonnet and EuroSCORE at the Heart Institute - USP. Rev Bras Cir Cardiovasc. 2012;27(2):187-94.
5. Mejía OA, Lisboa LA, Puig LB, Moreira LF, Dallan LA, Pomerantzeff PM, et al. InsCor: a simple and accurate method for risk assessment in heart surgery. Arq Bras Cardiol. 2013;100(3):246-54.
6. Mejía OA, Lisboa LA, Dallan LA, Pomerantzeff PM, Trindade EM, Jatene FB, et al. Heart surgery programs innovation using surgical risk stratification at the São Paulo State Public Healthcare System: SP-SCORE-SUS STUDY. Rev Bras Cir Cardiovasc. 2013;28(2):263-9.
7. Furie SS, Gutierrez MA, Figueiredo J, Tachinardi U, Rebelo MS, Bertozzo N, et al. Electronic Patient Record: integrating clinical information and image data. Rev. Bras. Eng. Biomed. 2003;19(3):125-37.
8. Lisboa LAF, Moreira LFP, Mejia OV, Dallan LAO, Pomerantzeff PMA, Costa R, et al. Evolution of cardiovascular surgery at the Instituto do Coração: analysis of 71,305 surgeries. Arq Bras Cardiol. 2010;94(2):162-8.
9. Mejía OA, Lisboa LA, Jatene FB. Continuous quality improvement programme in cardiovascular surgery: the Latin American perspective. Eur J Cardiothorac Surg. 2016;50(1):4-5.
10. Hannan EL, Cozzens K, King SB 3rd, Walford G, Shah NR. The New York State cardiac registries: history, contributions, limitations, and lessons for future efforts to assess and publicly report healthcare outcomes. J Am Coll Cardiol. 2012;59(25):2309-16.
11. Parsonnet V, Dean D, Bernstein AD. A method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. Circulation. 1989;79(6 Pt2):I3-12.
12. Ferguson TB Jr, Peterson ED, Coombs LP, Eiken MC, Carey ML, Grover FL, et al. Use of continuous quality improvement to increase use of process measures in patients undergoing coronary artery bypass graft surgery: a randomized controlled trial. JAMA. 2003;290(1):49-56.
13. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation (EuroSCORE). Eur J Cardiothorac Surg. 1999;16(1):9-13.
14. Clark RE. The STS Cardiac Surgery National Database: an update. Ann Thorac Surg. 1995;59(6):1376-80.
15. Hickey GL, Grant SW, Murphy GJ, Bhabra M, Pagano D, McAllister K, et al. Dynamic trends in cardiac surgery: why the logistic EuroSCORE is no longer suitable for contemporary cardiac surgery and implications for future risk models. Eur J Cardiothorac Surg. 2013;43(6):1146-52.
16. Kappetein AP. The bright future of cardiothoracic and vascular surgery: the role of EACTS. Eur J Cardiothorac Surg. 2013;43(1):211-4.
17. Ricciardi R, Virnig BA, Ogilvie JW Jr, Dahlberg PS, Selker HP, Baxter NN. Volume-outcome relationship for coronary artery bypass grafting in an era of decreasing volume. Arch Surg. 2008;143(4):338-44.
18. Hueb W, Lopes N, Gersh BJ, Soares PR, Ribeiro EE, Pereira AC, et al. Ten-year follow-up survival of the Medicine, Angioplasty, or Surgery Study (MASS II): a randomized controlled clinical trial of 3 therapeutic strategies for multivessel coronary artery disease. Circulation. 2010;122(10):949-57.
19. Authors/Task Force members, Windecker S, Kolh P, Alfonso F, Collet JP, Cremer J, et al. 2014 ESC/EACTS Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS)Developed with the special contribution of the European Association of Percutaneous Cardiovascular Interventions (EAPCI). Eur Heart J. 2014;35(37):2541-619.
20. LaPar DJ, Filardo G, Crosby IK, Speir AM, Rich JB, Kron IL, et al. The challenge of achieving 1% operative mortality for coronary artery bypasses grafting: a multi-institution Society of Thoracic Surgeons Database analysis. J Thorac Cardiovasc Surg. 2014;148(6):2686-96.
21. Evangelista A, Isselbacher EM, Bossone E, Gleason TG, Eusanio MD, Sechtem U, et al. Insights from the International Registry of Acute Aortic Dissection: a 20-year experience of collaborative clinical research. Circulation. 2018;137(17):1846-60.
22. Casalino R, Tarasoutchi F, Spina G, Katz M, Bacelar A, Sampaio R, et al. EuroSCORE models in a cohort of patients with valvular heart disease and a high prevalence of rheumatic fever submit-ted to surgical procedures. PLoS One. 2015;10(2):e0118357.

23. Piegas LS, Bittar OJ, Haddad N. Myocardial revascularization surgery (MRS): results from National Health System (SUS). Arq Bras Cardiol. 2009;93(5):555-60.

24. Stamou SC, Turner SL, Stiegel MR, Reames MK, Skipper E, Watts LT, et al. Quality improvement program decreases mortality after cardiac surgery. J Thorac Cardiovasc Surg. 2008;136(2):494-9.

25. Shahian DM, O'Brien SM, Normand SL, Peterson ED, Edwards FH. Association of hospital coronary artery bypass volume with processes of care, mortality, morbidity, and the Society of Thoracic Surgeons composite quality score. J Thorac Cardiovasc Surg. 2010;139(2):273-82.

26. Kurlansky PA, Argenziano M, Dunton R, Lancey R, Nast E, Stewart A, et al. Quality, not volume, determines outcome of coronary artery bypass surgery in a university-based community hospital network. J Thorac Cardiovasc Surg. 2012;143(2):287-93.

27. Miyata H, Motomura N, MurakamiA, Takamoto S, Japan Cardiovascular Surgery Database. Effect of benchmarking projects on outcomes of coronary artery bypass graft surgery: challenges and prospects regarding the quality improvement initiative. J Thorac Cardiovasc Surg. 2012;143(6):1364-69.

28. Hu S, Zheng Z, Yuan X, Wang Y, Normand SL, Ross JS, et al. Coronary artery bypass graft: contemporary heart surgery center performance in China. Circ Cardiovasc Qual Outcomes. 2012;5(2):214-21.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

How Do We Know a Change is an Improvement? The (Not So) New Scientific Knowledge Every Physician Should Learn, Master and Lead

Alexandre Siciliano Colafranceschi[1,2,3]

Universidade Federal do Estado do Rio de Janeiro,[1] *Rio de Janeiro, RJ - Brazil*
Instituto Nacional de Cardiologia,[2] *Rio de Janeiro, RJ - Brazil*
Hospital Pró Cardíaco,[3] *Rio de Janeiro, RJ – Brazil*

Short Editorial related to the article: Analysis of >100,000 Cardiovascular Surgeries Performed at the Heart Institute and a New Era of Outcomes

Cardiothoracic surgeons have a rich history of quality improvement and a strong ethos of transparency and innovation allowing for the rapid diffusion of standards, techniques, and benchmarks worldwide. Nationally, few medical specialties have contributed as much to the development of knowledge as the Brazilian cardiac surgery. From the hard work developed during decades by pioneering surgeons such as Euryclides Zerbini and Adib Jatene to the most contemporaneous leaders in the field, the *Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo* – InCor – is definitely at the heart of this journey.[1] In this issue of *Arquivos Brasileiros de Cardiologia* the work by Mejia et al.[2] has the merit of taking into account the evolution of the number of cardiovascular surgeries performed at InCor during a 35-year period. The total number is a remarkable one: over 100,000 open heart procedures were analyzed. After all, the mean number of procedures/year is 2,964, - or more than 11 procedures per workday. It is noteworthy the fact that the total number of procedures has been increasing, especially due to an increase in valvular operations and the correction of congenital cardiopathies. Also, of note, there is a 7% decrease in coronary artery bypass graft surgery volume in the most recent period studied.

Besides describing the volume of disease-specific open-heart surgical procedures throughout five different periods of time over the 35 years of data, another objective of the study by Mejia et al.[2] was to evaluate the impact of the actions taken from a continuous quality improvement program on mortality from cardiovascular surgery. It is not clear, however, how the periods of time were selected for the analyses.

The quality improvement initiative at InCor, called *Programa de Melhoria Contínua da Qualidade (PMCQ),* was consolidated in 2016 with a clear mission to decrease the cardiovascular surgical operative mortality. It is hosted at the *Unidade Cirúrgica de Qualidade e Segurança do Paciente Cirúrgico (UCQSP)* as a department of the Cardiovascular Surgical Division at InCor. According to the authors, this unit aims to support the construction of the safety culture, promote transparency, standardize training, improve the work of the teams and monitor the surgical performance.[2]

When InCor aims to support the construction of a safety culture, it is clear that they head toward the right direction. As stated by Robert Lloyd,[3] Vice President at the Institute for Healthcare Improvement, "Quality" is not a department. An organization will only make meaningful and sustainable improvements when people at every level feel a shared desire and responsibility for making processes and outcomes better every day.

After analyzing the data, the authors concluded that there was a significant decrease in operative mortality (closer to international standards) in the studied groups after the implementation of the quality improvement program at InCor. The question that remains is how do we know that the changes made after the PMCQ consolidation resulted in an improvement in surgical mortality?

Directing efforts in collecting, analyzing and applying data of the surgical results in order to improve quality and reassess conducts and procedures is critical to quality improvement initiatives. Mixing accountability or research measures with those for improvement, however, is counterproductive.[4]

Modern Quality Improvement (QI) concepts had their origins in the Statistical Process Control (SPC) measurements developed by Walter Shewart in the 1920s. The marriage of those techniques with an overall management philosophy by Edwards Deming, Joseph Juran, and others has resulted in the quality movement as it is known through various terms and acronyms (TQM – Total Quality Management, CQI – Continuous Quality Improvement, and so on). Although arriving later in health care than in other fields, QI concepts have rapidly proliferated here through the efforts of Berwick and others.[5]

Quality improvement requires using data to learn and to predict future performance (as opposed to what happened in the past, as stated by accountability and research data). Regarding improvement, it is critical to understand that every process has an inherent variation that one wants to understand. Understanding the terms process and variation, besides developing process thinking, are fundamental to an understanding of how to improve anything.

Contemporary cardiothoracic surgical care is a complex process, involving sophisticated techniques and equipment, health care professionals with varying levels of skills, and high-risk patients. Surgeons work in a safety-critical environments where the complexity of care and the patients' risk factors exponentially increase the potential for significant harm. The designed system of caring for surgical patients deliver

keywords

Cardiovascular Surgical Procedures/trends; Quality Improvement; Patient Safety; Hospital Mortality; Database.

Mailing Address: Alexandre Siciliano Colafranceschi •
Instituto Nacional de Cardiologia - Cirurgia Cardíaca - Rua das Larangeiras, 374. CEP 22240-002, Rio de Janeiro, RJ – Brazil
E-mail: alexandre.siciliano@gmail.com

DOI: https://doi.org/10.36660/abc.20200249

outcomes that vary throughout time, irrespective of being successful or not. Because humans and poorly designed systems are vulnerable to error, a critical assessment of our systems of care is essential for improvement to continue.[6]

Variation in a quality measure may result from *common causes* — expected causes that are inherent to the system. It may also derive from *special causes* — unnatural causes that are not part of the system but arise due to specific circumstances.

There are many ways to present and analyze data. For improvement efforts, a *control chart* (Figure 1) helps distinguish between special and common causes of variation. It includes an upper control limit and a lower control limit marked above and below the average line. Variation within these limits is expected and attributed to common causes; variation beyond these limits suggests special causes.[7]

In a stable system, only common causes affect the outcomes. Variation is predictable within statistically established limits. By contrast, in an unstable system, outcomes are affected by both common causes and special causes. In this case, variation is unpredictable. If the process is stable and variation is predictable, one can foresee the future outcome for the system being observed in real-time, which makes it suitable for improvement efforts. *Control charts* can also be used to identify early signs of success in an improvement project and to monitor a process to ensure it is holding the gains from a quality improvement effort. Like a *run chart* it helps determine whether the changes made are leading to improvement. The point here is that improvement efforts can only be made in stable systems.[7]

Data driven from the original manuscript in its tables 1 and 2 (total volume of procedures and total operative death index throughout different periods of time) were used to build a control chart as in Figure 1. Statistical process control (SPC) techniques have played an efficacious role in monitoring hospital performance, such as mortality rate.[6] According to this analysis, the system being used for improvement efforts in the work by Mejia et al.[2] is an unstable system and the outcome (operative death) is affected by both common and special causes. Since variation is unpredictable in an unstable system, the changes from PMCQ at InCor cannot be attributed to the improvement in total operative death from period 4 to period 5. In fact, using SPC methodology, there is no difference in operative mortality between periods 1,2,3 and 5. The operative mortality at InCor has been varying close to international standards since they started collecting these data. A special cause in period 4 increased the operative mortality beyond the upper control limit, which made it statistically different from period 5, when research statistical methods were used to analyze an improvement effort.

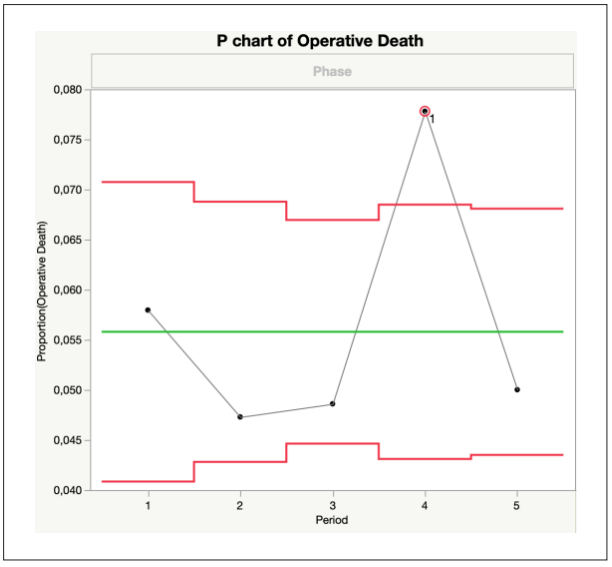


Figure 1 - *P chart of operative death. Data obtained from tables 1 and 2 of the original manuscript. Average line is in green. Upper and lower control limits are in red. Dots represents the operative death index for the specified period of time. Dots are connected in a black line that shows variation. Operative death in period 4 is beyond the upper control limit (as marked in a red circle), suggesting a special cause in the process of caring within this period of data collection.*

Health care organizations use data to understand their performance — although they do not always do so effectively.[4] It is important to note that the quality improvement staff view and seek to use data regarding variation in healthcare processes differently from that of health services researchers. Where practical, real-time quality improvement is the goal, variation itself needs to be examined in real time to answer the questions: 1- Are we getting better? And 2- Where can we improve?[4] Thus, "just-in-time" performance data are essential to the effective use of variation data, and the focus is on creating stable processes and learning from special-cause variation. In contrast, health services researchers pose the question, does A cause B (other things being equal?), often taking the long view to examine several years` worth of data and seeking to eliminate special-cause variation and test for significance.[8] These different perspectives can lead healthcare managers and researchers to look at the same results and reach very different conclusions about their significance and the actions that should be taken in response.[4]

Learning fast from mistakes is part of the improvement theories and although there was no proven improvement in operative mortality attributed to actions taken after PMCQ consolidation, the continuous quality improvement effort at InCor is far from being unsuccessful. The PMCQ initiative at InCor should be followed by others. InCor not only pioneered and mastered the open-heart surgical academy in the country. Its leadership in the field continues to change our own perspectives regarding what means to be a contemporary heart surgeon within a system. InCor is helping us reflect on the traditional view that patient outcomes are related only to the surgeon's technical skill to an evolving and broader framework, wherein health care outcomes are affected by a multitude of factors in highly integrated and complex processes and environment. Since physicians (and surgeons) are involved in almost all-important health care processes, it is wasteful to try to improve health care processes without them.[5] It is still required for a surgeon to learn, master and lead the current and new technology and technical skills to care for patients. Contemporarily, however, this is not sufficient to improve outcomes. It is time for cardiothoracic surgeons (and every physician) to reflect on their own personal purposes of being a healthcare professional and learn, master and lead the (not so) new scientific knowledge to improve patient outcomes.

References

1. Braile D, Gomes CJ. Evolution of cardiovascular surgery: the Brazilian saga. A history of work, pioneering experience and success. Arq Bras Cardiol. 2010;94(2):151-2.
2. Mejia OAV, Lisboa LAF, Caneo FF, Arita E T, Brandão CMA, Dias RR, et al. Análise de >100.000 cirurgias cardiovasculares realizadas no Instituto do Coração e a nova era com foco nos resultados. Arq Bras Cardiol. 2020; 114(4):603-612.
3. Solberg LI, Mosser G, McDonald S. *The Three Faces of Performance Measurement: Improvement, Accountability, and Research. The Joint Commission Journal on Quality Improvement. 19(7;23(3):135-47.*
4. Berwick DM. Continuous improvement as an ideal in health care. N Engl J Med. *1989*;320(1):53-6.
5. Sanchez, JÁ; Ferdinand, FD; Fann, JI. Patient Safety in Cardiothoracic Surgery. An Overview. Ann Thorac Surg. 2016;101(2):426-33.
6. Suman GS, Prajapati D. Control chart applications in healthcare: a literature review. Int J Metrol Qual Eng. 2018;9(5):1-21.
7. *Neuhauser* D, *Provost* L, *Bergman* B. The meaning of variation to healthcare managers, clinical and health-services researchers, and individual patients. BMJ Qual Saf. *2011* Apr;20(Suppl 1):i36-40.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Ser49Gly Beta1-Adrenergic Receptor Genetic Polymorphism as a Death Predictor in Brazilian Patients with Heart Failure

Felipe Neves de Albuquerque,[1,2] Andrea Araujo Brandão,[1] Dayse Aparecida Silva,[3] Ricardo Mourilhe Rocha,[1] Marcelo Imbroinise Bittencourt,[1] Ana Luiza Ferreira Sales,[1] Pedro Pimenta de Mello Spineti,[1] Gustavo Salgado Duque,[1] Lucas Rangel de Souza Azevedo,[1] Roberto Pozzan,[1] Bernardo Rangel Tura,[4] Denilson Campos de Albuquerque,[1]

Universidade do Estado do Rio de Janeiro,[1] Rio de Janeiro, RJ – Brazil

Hospital Samaritano,[2] Rio de Janeiro, RJ – Brazil

Universidade do Estado do Rio de Janeiro - Instituto de Biologia,[3] Rio de Janeiro, RJ – Brazil

Instituto Nacional de Cardiologia – Arritmia,[6] Rio de Janeiro, RJ – Brazil

Abstract

Background: **The role of Ser49Gly beta1-adrenergic receptor genetic polymorphism (ADBR1-GP-Ser49Gly) as a predictor of death in heart failure (HF) is not established for the Brazilian population.**

Objectives: **To evaluate the association between ADBR1-GP-Ser49Gly and clinical outcomes in individuals with HF with reduced ejection fraction.**

Methods: **Secondary analysis of medical records of 178 patients and genotypes of GPRβ1-Ser49Gly variants, classified as Ser-Ser, Ser-Gly and Gly-Gly. To evaluate their association with clinical outcome. A significance level of 5% was adopted.**

Results: **Cohort means were: clinical follow-up 6.7 years, age 63.5 years, 64.6% of men and 55.1% of whites. HF etiologies were predominantly ischemic (31.5%), idiopathic (23.6%) and hypertensive (15.7%). The genetic profile was distributed as follows: 122 Ser-Ser (68.5%), 52 Ser-Gly (28.7%) and 5 Gly-Gly (2.8%). There was a significant association between these genotypes and mean NYHA functional class at the end of follow-up (p = 0.014) with Gly-Gly being associated with less advanced NYHA. In relation to the clinical outcomes, there was a significant association (p = 0.026) between mortality and GPRβ1-Ser49Gly: the number of deaths in patients with Ser-Gly (12) or Gly-Gly (1) was lower than in those with Ser-Ser (54). The Gly allele had an independent protective effect maintained after multivariate analysis and was associated with a reduction of 63% in the risk of death (p = 0.03; Odds Ratio 0.37 – CI 0.15–0.91).**

Conclusion: **The presence of β1-AR-GP Gly-Gly was associated with better clinical outcome evaluated by NYHA functional class and was a predictor of lower risk of mortality, regardless of other factors, in a 6.7-year of follow-up. (Arq Bras Cardiol. 2020; 114(4):613-615)**

Keywords: **Heart Failure/mortality;Epidemiology; Polymorfism, Geetic; Receptors,Adreneic, beta; cardiovascular Dieases; Hospitalization; Epinephrine/therapeutic use; Cardiotoxicity.**

Introduction

Heart failure (HF) is currently the main cause of hospital admissions due to circulatory diseases in the Brazilian public healthcare system: 202,000 patients were admitted in 2018, costing BRL 311 million.[1]

The current strategy with clinical, laboratory and imaging parameters to predict prognosis is limited. The natural history of HF is unpredictable, even in phenotypically similar patients.

Mailing Address: Felipe Neves de Albuquerque •
Universidade do Estado do Rio de Janeiro – Cardiologia - Boulevard 28 de Setembro, 77, 2º andar. Postal Code 20550-900, Rio de Janeiro, RJ - Brazil
E-mail: felipenalbuquerque@gmail.com, felipe.albuquerque@uerj.br
Manuscript received March 20, 2019, revised manusacript June 04, 2019, accepted June 05, 2019

DOI: https://doi.org/10.36660/abc.20190187

The therapies available are capable of reducing mortality by up to 60%,[2] but response to these medical treatments is heterogeneous. It has been demonstrated that genetic nature influences this variability.[3-5]

In the pathophysiology of HF, the role of the Sympathetic Nervous System (SNS) is well established. Cardiac beta1-adrenergic receptor (Rβ1) is the main structure responsible for mediating the effects of adrenaline. Sustained stimulation of this system determines multiple deleterious effects,[3] especially cardiotoxicity.[6]

Accordingly, some genetic variants that modified the activity of this receptor have been described. A genetic polymorphism (GP) was identified at position 145 of the nucleotide that resulted in the substitution of Serine for Glycine at position 49 of the amino acid – GPRβ1-Ser49Gly.[7]

GPRβ1-Ser49Gly was associated with a dramatic interference with Rβ1 function. The Gly allele determined greater reduction in its number (down-regulation) compared

with the Ser allele.[6,7] Because of the continuous exposure to adrenaline, this dysfunction could be clinically relevant in HF. In practice, this genetic mutation would determine desensitization with a relevant intrinsic adrenergic block.[8]

Accordingly, in the context of HF, some publications analyzed GPRβ1-Ser49Gly in scenarios that included: risk of HF,[3,9-11] beta-blocker response,[6,12] echocardiographic outcomes,[13] functional capacity,[14] cardiac arrhythmia[10,15] and clinical outcomes.[7,16,17] These studies include a small number of patients and present some inconsistent findings. In general, the Gly allele was associated with better clinical outcome;[7,17] however, a potential influence of ethnicity on these genotypes was observed, inverting this benign behavior in some populations.[9] For these reasons, the role of this genotype is still unknown.

Therefore, it is of paramount importance to analyze the behavior of this GP in a Brazilian population with its own ethnic characteristics, in order to establish the pattern of this GP for our population, increasing our (small) current genetic database.[10,16]

The objective of this study is to evaluate the association between the Ser49Gly genotypes and major clinical outcomes, such as hospital admissions due to HF and death in individuals with HF with reduced ejection fraction.

Methods

Study design

Longitudinal study of a cohort of patients. Information was collected from medical records dated between January 2015 and April 2018, since the beginning of follow-up. All patients were seen at the same HF clinic of a university hospital.

Study population

This is a series of cases followed for 6.7 years, which consecutively included 178 patients (113 men and 65 women) diagnosed with HF with reduced ejection fraction, being characterized as a convenience sampling.

Inclusion criteria

Patients aged 18 or older, with symptomatic HF (defined by the Framingham criteria), systolic ventricular dysfunction and left ventricular ejection fraction (LVEF) ≤ 50% on two-dimensional echocardiography.

Exclusion criteria

Patients with unknown clinical status at the end of the study.

Method

Statistical analysis

Statistical analysis was performed using SPSS for Mac, version 25. For all of the tests, 0.05 or 5% ($p < 0.05$) was defined as the rejection level of the null hypothesis and 95% confidence interval (CI). The measures of central tendency were expressed as mean ± standard deviation. Categorical variables were expressed in absolute and relative frequencies n(%).

The following statistical tests were used: One-way ANOVA complemented by Tukey's test, chi-square test and logistic regression. To evaluate the homogeneity of variances, Levene's test was used. When there was no homogeneity of variances, the Kruskal-Wallis test was used to compare the means of three or more independent samples and Mann-Whitney test was used for up to two independent samples.

Binary logistic regression was used to evaluate the clinical outcomes studied. Initially, the variables were evaluated separately in order to identify which ones were statistically relevant. Subsequently, they were evaluated together as covariables. A 95% significance level was considered for entry in the model and 90% for the removal of variables in the stepwise method of choice.

Heart failure etiology

The etiologies were classified into five groups: ischemic, idiopathic, hypertensive, alcoholic and others. The attending physician at the HF service was in charge of defining the etiology according to previously established criteria.[18]

Clinical, laboratory and echocardiographic parameters

Skin color was determined by the attending physician and classified as white, black or other. Functional class was determined according to the New York Heart Association (NYHA) at the beginning and at the end of follow-up. Death registries were taken from the medical records and, if no records were available, an active search was conducted on the electronic medical records, by phone call or on death certificate databases available on the Internet.

The most recent laboratory tests were considered for statistical analysis.

All individuals had their electrocardiograms (ECG) analyzed for QRS duration, presence of left bundle branch block and atrial fibrillation.

Echocardiographic variables

The parameters evaluated were: LV systolic diameter, LV diastolic diameter and LV ejection fraction. Two tests were used: one at the beginning and another at the end of follow-up.

Genotyping

Genotyping was performed using polymerase chain reaction and restriction fragment length polymorphism (PCR-RFLP) for the Rβ1 gene: 49Ser>Gly polymorphism. The details of these procedures followed specific literature.[19]

All individuals were tested for the presence of Ser (wild and most common) and Gly (recessive) alleles. Based on the presence of these alleles, the individuals were classified into Ser-Ser, Ser-Gly and Gly-Gly.

Gene and haplotype frequencies were tested for the Hardy-Weinberg equilibrium,[20] using the software ARLEQUIN version 2000.

The project was approved by the Research Ethics Committee of Hospital Universitário Pedro Ernesto on 12/16/2009. An Informed Consent Form (ICF) was signed by all patients.

This study was partially funded by FAPERJ (Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro).

Results

Characteristics of the sample population and GP-Rβ1

Table 1 shows the general characteristics of the study population. Mean age of 64.4 ± 12.8 years (variation: 24–93 years), a higher prevalence of males, white skin color and ischemic etiology were observed.

The mean follow-up time at the HF clinic was 6.7 ± 4.4 years.

As for the genetic profile, the Ser allele occurred 295 times (82.8%) whereas the Gly allele occurred 61 times (17.2%). In relation to the genotypes, 122 (68.5%) were classified as Ser-Ser, 51 (28.7%) as Ser-Gly and only 5 (2.8%) as Gly-Gly.

A significant difference (p = 0.003) was found between GP-Rβ1 and skin color: there was a higher prevalence of whites among those with Ser-Ser genotype and virtually an equilibrium between Ser-Gly individuals with white skin and others, as shown in Table 1.

The population was in genetic equilibrium, according to the Hardy-Weinberg theorem.[20]

There were no significant differences between the genotypes regarding clinical characteristics, baseline NYHA functional class, electrocardiographic, echocardiographic and laboratory characteristics or medical treatment, as shown in Table 1.

Clinical outcome

Clinical outcome data are shown in Table 2.

The Rβ1 genotype showed a significant association with the final NYHA functional class (p = 0.014), with Ser-Ser being associated with the most advanced functional class. Of the eighteen NYHA IV patients, Ser-Ser was found in 88.9% of the cases. The Ser-Gly GP was responsible for the other two cases. All five patients with Gly-Gly genotype progressed with NYHA I or II at the end of the follow-up.

Mean NYHA functional class was lower than baseline (2.15 ± 0.9 → 2.02 ± 1.0). As for outcomes, 24.9% showed improved functional class, 38.4% remained stable and 36.7% showed NYHA worsening. There was no significant difference between GP-Rβ1 and NYHA mean values or change in functional class during clinical follow-up.

Outcomes: Deaths and hospital admissions due to HF

The clinical outcomes of hospital admission due to HF and death were investigated both separately and in association.

Combined outcome of admission due to HF+Death occurred in 100 patients (56.2%). It was more frequent in the Ser-Ser group (60.7%) with no significant difference when comparing Ser-Gly (47.1%) with Gly-Gly (40.0%) cases.

In relation to the number of hospitalizations alone, 182 events were observed in 74 patients, with no significant difference between GP-Rβ1 types.

Finally, deaths only were analyzed: 67 events – an overall mortality rate of 37.6%. The Ser-Ser genotype accounted for 80.5% of these deaths and only 1.5% of patients who died had the Gly-Gly genotype. In the comparative analysis of the distribution of deaths by GP, there was a significant difference (p = 0.026) between the genotypes Ser-Ser, Ser-Gly and Gly-Gly, with mortality rates of 44.3%, 23.5% and 20.0%, respectively. Table 2 and Figure 1 depict these findings.

The impact of GP-Rβ1 on the mortality of these patients was shown through multivariate analysis: the Gly allele had a protective effect independent of other factors after adjustment for final NYHA, final LVEF, creatinine, low adherence and final heart rate. The presence of each copy of the Gly allele was associated with risk of death reduced by 63% (p = 0.03; Odds Ratio 0.37 – CI 0.15–0.91). These data are shown in Table 3.

The cause of death was determined in 56% (34) of the cases: 61.8% were related to HF worsening, 29.4% of sudden deaths and 8.8% due to other causes. There was no difference between the genotypes regarding the cause of death.

Discussion

This study describes the association between the Beta-1 Genetic Polymorphism Ser49Gly genotypes and clinical outcome in 178 patients with HF, with mean follow-up of 6.7 years. Of all the studies published on Ser49Gly genotyping in the context of HF, this one has the longest follow-up time. Its main finding was the association of Gly-Gly GP-Rβ1 with a protective effect for clinical outcomes, with better clinical outcome evaluated by NYHA functional class and lower risk of death.

When we compared with other Brazilian populations, we found a relatively similar allelic distribution: the Gly allele was present in 13 to 17% of the HF cases.[10,16] In relation to the genotypes, it was largely similar to a study including 201 patients from the state of Rio Grande do Sul[10] but different from the cohort of 146 patients from the municipality of Niterói, in the state of Rio de Janeiro.[16]

Due to the intense miscegenation of the Brazilian population, skin color is probably not a good determinant of the genetic profile, as despite the similarity in the percentage of whites between this study and that of Pereira et al.,[16] there is a difference in their genetic profile. Thus, ethnicity assessed by skin color alone could not explain the high percentage of the Gly-Gly genotype found by Pereira et al.[16] Stressing this point, international studies have shown a strong similarity with this cohort, as to the genotypic distribution of GP-Rβ1:[7,9,17] 63 to 73% of Ser-Ser, 27 to 35% of Ser-Gly and 0 to 3% of Gly-Gly individuals, although the studies included other ethnicities. It may be worth conducting other national studies in order to evaluate the genotypic distribution of this genetic polymorphism in our population.

Table 1 — Baseline characteristics of the population according to the genetic polymorphisms of Ser49Gly β1-adrenergic receptor

Clinical Variable*		Total	Ser49Gly β1 Genetic Polymorphism			
			Ser-Ser (n = 122)	Ser-Gly (n = 51)	Gly-Gly (n = 5)	p
Men n %		113 (63.5%)	79 (64.8%)	31 (60.8%)	3 (60.0%)	0.873
Follow-up (years)		6.7 ± 4.4				
Duration of HF (months)		8.9 ± 6.1				
Age (years)		64.4 ± 12.8				
Skin Color	White	98 (55.1%)	76 (62.3%)	22 (43.1%)	0 (0.0%)	0.003
	Black	28 (15.7%)	20 (16.4%)	6 (11.8%)	2 (40.0%)	
	Other	52 (29.2%)	26 (24.3%)	23 (45.1%)	3 (60.0%)	
Etiology	CAD	56 (31.5%)	43 (35.2%)	12 (23.5%)	1 (20.0%)	0.093
	Idiopathic	42 (23.6%)	27 (22.1%)	13 (25.5%)	2 (40.0%)	
	Hypert	28 (15.7%)	13 (10.7%)	13 (25.5%)	2 (40.0%)	
	Alcohol	19 (10.7%)	12 (9.8%)	7 (13.7%)	0 (0.0%)	
	Other	33 (18.5%)	27 (22.1%)	6 (11.8%)	0 (0.0%)	
Baseline NYHA†	I	47 (26.6%)	36 (29.8%)	9 (17.6%)	2 (40.0%)	0.334
	II	70 (39.5%)	50 (41.3%)	19 (37.3%)	1 (20.0%)	
	III	47 (26.6%)	28 (23.1%)	17 (33.3%)	2 (40.0%)	
	IV	13 (7.3%)	7 (5.8%)	6 (11.8%)	0 (0.0%)	
	Mean	2.15 ± 0.9	2.05 ± 0.9	2.39 ± 0.9	2.0 ± 1.0	0.068
Baseline LVEF (%)		34.8 ± 10.7	35.3 ± 11.2	33.5 ± 8.1	37.4 ± 2.1	0.54
Hypert	n %	134 (75.7%)	88 (72.7%)	42 (82.4%)	4 (80.0%)	0.395
DM	n %	60 (33.7%)	39 (32.0%)	19 (37.3%)	2 (40.0%)	0.763
AF	n %	41 (24.0%)	29 (24.8%)	12 (24.5%)	0 (0.0%)	0.492
Lab	Hemoglobin (mg/dL)	13.2 ± 1.9	13.2 ± 2.0	13.1 ± 1.7	13.8 ± 2.2	0.734
	Sodium (mEq/L)	139.8 ± 3.4	139.9 ± 3.4	139.8 ± 3.3	139.0 ± 4.6	0.843
	Potassium (mEq/L)	4.47 ± 0.7	4.46 ± 0.7	4.52 ± 0.6	4.38 ± 0.5	0.836
	Creatinine (mg/dL)	1.41 ± 1.0	1.50 ± 1.1	1.23 ± 0.5	1.06 ± 0.2	0.199
Treatment	BB n %	173 (97.2%)	118 (96.7%)	50 (98.0%)	5 (100.0%)	0.828
	ACEI n %	79 (44.4%)	52 (42.6%)	23 (45.1%)	4 (80.0%)	0.255
	ARB n %	54 (30.3%)	37 (30.3%)	16 (31.4%)	1 (20.0%)	0.87
	Spiro n %	83 (46.6%)	52 (42.6%)	27 (52.9%)	4 (80.0%)	0.147
	Digox n %	47 (26.4%)	30 (24.6%)	15 (29.4%)	2 (40.0%)	0.631
	Low adherence n %	81 (46.0%)	52 (43.0%)	27 (54.0%)	2 (40.0%)	0.405
	Furosemide (dose-mg)	90.8 ± 64.3	97.3 ± 66.8	81.0 ± 59.8	55.0 ± 30.0	0.22

**Numerical variables are expressed as mean ± standard deviation; categorical variables expressed as [n e (%)]. Follow-up: follow-up time (in years); duration of HF: duration of disease course since the date of diagnosis (in years); CAD: Coronary Artery Disease; Hypert: Systemic Arterial Hypertension; NYHA: New York Heart Association Functional Class; LVEF: Left Ventricular Ejection Fraction; DM: Diabetes Mellitus; AF: Atrial Fibrillation; LBBB: Left Bundle Branch Block; Hb: Hemoglobin (in mg/dL); BB: Betablocker; ACEI: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; Spiro: Spironolactone; Digox: Digoxin. †Baseline NYHA class data were not available for 1 patient from the Ser-Ser group.*

Table 2 – Clinical outcomes according to the genetic polymorphisms of Ser49Gly β1-adrenergic receptor

Clinical Variable*		Total	Ser49Gly β1 Genetic Polymorphism			
			Ser-Ser (n = 122)	Ser-Gly (n = 51)	Gly-Gly (n = 5)	p
Final NYHA	I	68	42	24	2	**0.014**
		38.2%	34.4%	47.1%	40.0%	
	II	57	45	9	3	
		32.0%	36.9%	17.6%	60.0%	
	III	35	19	16	0	
		19.7%	15.6%	31.4%	0.0%	
	IV	18	16	2	0	
		10.1%	13.1%	3.9%	0.0%	
	Mean	2.02 ± 1.0	2.07 ± 1.0	1.92 ± 1.0	1.6 ± 0.5	0.420
Final LVEF (%)		35.4 ± 13.3	35.1 ± 13.2	35.8 ± 13.4	39.6 ± 16.2	0.751
Hospital admission	n	74	54	18	2	0.55
	%	41.6%	44.3%	35.3%	40.0%	
Death	n	67	54	12	1	**0.026**
	%	37.6%	44.3%	23.5%	20.0%	
Hospital admission + Death	n	100	74	24	2	0.197
	%	56.2%	60.7%	47.1%	40.0%	

**Numerical variables are expressed as mean ± standard deviation; categorical variables expressed as [n e (%)]. NYHA: New York Heart Association Functional Class;*

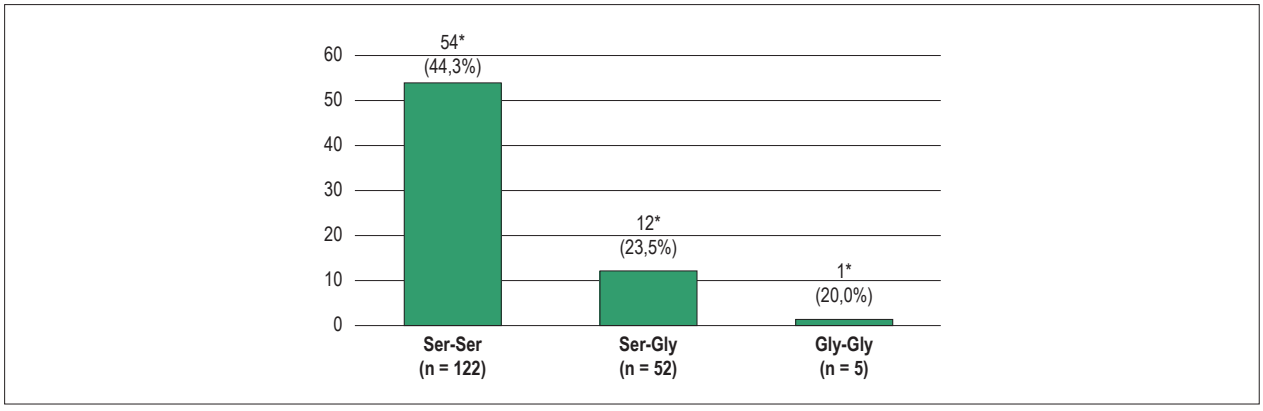


Figure 1 – *Distribution of number of deaths according to Ser49Glyβ1 genetic polymorphism. Data were expressed in absolute and relative frequencies. In the comparison of Ser-Ser x Ser-Gly x Gly-Gly genotypes: *p = 0.026, chi-square test.*

Table 3 – Multivariate Analysis: Predictors of death

Variable	p	Odds ratio
Copy of Gly allele	0.030	0.37 (0.15–0.91)
Final NYHA	0.002	2.14 (1.32–3.45)
Final LVEF	0.002	0.94 (0.91–0.98)
Creatinine	0.051	1.52 (1.00–2.31)
Low adherence	0.346	1.50 (0.65–3.46))
Final HR	0.124	1.03 (0.99–1.07)

NYHA: New York Heart Association Functional Class; LVEF: left ventricular ejection fraction; HR: heart rate.

Another even more relevant aspect is the clinical interpretation of this GP. In this case, it was possible to demonstrate that Gly-Gly had a significant association with a surrogate clinical marker: final NYHA (p = 0.014). Individuals with this genotype had a better clinical outcome: no patient in this group showed advanced functional class at the end of the follow-up. Although it is a relatively small number of patients (five individuals), the longer follow-up time compared with other studies allowed the distinction of clinical behaviors among the genotypes.

Considering that there were no baseline clinical differences among the three GPs, including treatment, the difference in the final NYHA found in this study suggests that genetic variations could influence the pathophysiology of heart disease. Therefore, genotyping could identify a subgroup of patients with HF with worse clinical outcome.

This finding is an original one in the literature, as there are no publications on patients with HF correlating GPRβ1-Ser49Gly to clinical outcomes, such as NYHA functional class. Because of that, it is not possible to compare this result with other populations, which would be appropriate to validate this finding.

Despite its recognized prognostic value, NYHA functional class is an inaccurate marker of HF severity. The lack of inter-examiner reproducibility has been described and may limit its accuracy.[21] It also translates only one clinical aspect of the syndrome. In the future, it may be more appropriate to study the association of the genotype with more complete clinical scores, such as MAGGIC,[22] in which there is a combination of clinical, laboratory and echocardiographic variables.

The high mortality rate found in this study – 37.6% – is probably due to the long follow-up time. For comparison purposes, Biolo et al.[10] found a mortality rate of 27.9% in Rio Grande do Sul and Pereira et al.[16] found 12.3% in Rio de Janeiro. Despite the disparity between these rates, there are similarities in the baseline characteristics of these populations: LVEF of approximately 30–35%, the majority (65–75%) of patients in NYHA I or II and an optimized therapy adopted. The most significant difference between the three studies is their follow-up time: 80.4 months in this study, and 39.8 months[10] and 23 months[16] in the abovementioned studies, respectively.

Assessment of the association of GP-Rβ1 with mortality showed that the wild Ser-Ser allele concentrated most of these events and the Gly allele was consistently associated with a protective effect. The presence of each copy of the Gly allele was associated with a 63% reduction in the risk of death. This protective effect was maintained even after strict adjustment for the main variables used to stratify HF prognosis. Accordingly, in a hybrid model that incorporated genetic, clinical, laboratory, echocardiographic, treatment and physical examination variables, Gly-Gly remained with a high predictive value for the lower occurrence of deaths.

In the literature review, the results are diverse, but mostly consistent with the current one. Those include studies that have found no association between GPRβ1-Ser49Gly and clinical outcomes,[10,16,23] studies with the same protective pattern as the Gly allele[7,17,24] and even a paper paradoxically associating Gly with poor prognosis in HF.[13]

In line with our findings, the first studies of Borjesson et al.[7] (the first description of this GPRβ1-Ser49Gly), Forleo et al.[24] and Magnusson et al.[17] describe the protective profile of the Gly allele: significantly fewer deaths were observed with the genotypes Ser-Gly or Gly-Gly, even after adjusting for other variables.

However, there is a study describing the opposite, i.e., the Gly allele associated with poor prognosis. Wang et al.[13] described GPR1-Ser49Gly in a Chinese population of 430 patients with HF and baseline characteristics similar to those of this study. The authors associated the Gly allele to worse echocardiographic outcomes and higher mortality.

The contrast between these findings may be related to a different genetic impact on the ethnicities. Two pieces of evidence underlie this theory. Firstly, Pereira et al.[16] identified Ser-Ser as a factor of poor prognosis in a multi-ethnic population from the city of Niterói, state of Rio de Janeiro. Nevertheless, this pattern was only found in patients with black skin. This finding was also reproduced in the meta-analysis of Liu et al.[9] The analysis of 2,979 patients genotyped for Ar389Gly and Ser49Gly GP-Rβ1 identified a specific pattern of the Gly389 allele for each ethnicity: association with higher risk of HF in Asian patients, while in whites, it was associated with a reduction of this risk.

Along the same lines, the A-HEFT study described better response to nitrate and hydralazine combination for African-American patients.[25] Subsequently, McNamara et al. associated this benefit to a particular GP of Nitric Oxide Synthase, more frequent in African Americans compared to whites.[26]

Likewise, the meta-analysis of Liu et al.[9] and the study by McNamara et al.[26] describe the variety of clinical effects among different ethnicities in the context of HF. This reinforces the need for specific studies targeted at Brazilian patients, as the behavior of these GPs for a population that is recognized as miscegenated is unpredictable.

These examples reaffirm the genetic influence on the natural history of HF. Generally speaking, we acknowledge the pathophysiological response of the syndrome as a result of the activation of hormonal systems. However, at the molecular level, beta-adrenergic receptors and enzymes, such as nitric oxide synthase, are some of the important factors implicated in cardiac remodeling. The functional modification of these and other agents due to genetic polymorphisms may explain these multiple clinical outcomes in phenotypically similar patients.

The process of neurohumoral response involves a multitude of elements, each potentially sensitive to diverse genetic mutations. In view of that, a genetic panel including the main systems (sympathetic nervous system, renin-angiotensin-aldosterone system and atrial natriuretic peptide) is likely to be more appropriate than a specific isolated polymorphism. The first step is to identify the main genetic markers for each system. In relation to the sympathetic nervous system and the beta-adrenergic receptor, this study stresses the prominent role of the Ser49Gly GP.

In the future, the construction of a multisystemic genetic score may prove to be a powerful prognostic predictor. Possibly, a score capable of identifying high-risk individuals, even at the onset of disease, when clinical findings and complementary tests are not yet significantly abnormal.

The relatively small number of patients (178) is a limitation in this study and may have influenced the results, especially due to the low number of patients with the Gly-Gly genotype. However, the genotypic distribution pattern observed was the same in most studies and this is the study with the longest follow-up time with GP-Rβ1 in the context of HF. It is also worth noting that, despite this reduced number, it was possible to find results with statistical significance.

Another limitation refers to the collection of data from medical records. However, since all individuals are followed at a HF clinic, standardization of care routines and information records, as well as the care provided by the doctors involved with the treatment and follow-up of this syndrome, ensured higher quality of the information obtained. Nevertheless, if hospitalization occurred in another institution, there was no access to information and even the number of hospitalizations may be underestimated. This may have determined the absence of statistical differences between the genotypes and limited the evaluation of this clinical outcome.

Conclusions

In patients with HF with reduced ejection fraction, the presence of Gly-Gly GP-Rβ1 was associated with better clinical outcome assessed by NYHA functional class and was a predictor of lower risk of mortality, regardless of other factors in 6.7 years of follow-up.

Author contributions

Conception and design of the research: Albuquerque FN, Brandão AA, Mourilhe-Rocha R; Acquisition of data: Albuquerque FN, Silva DA, Bittencourt MI; Analysis and interpretation of the data: Albuquerque FN, Brandão AA; Statistical analysis: Albuquerque FN, Pozzan R; Obtaining financing: Albuquerque FN; Writing of the manuscript Albuquerque FN, Brandão AA, Bittencourt MI; Critical revision of the manuscript for intellectual content: Albuquerque FN, Brandão AA, Bittencourt MI, Sales ALF, Spineti PPM, Duque GS, Albuquerque D.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by FAPERJ (Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro).

Study Association

This article is part of the thesis of Doctoral submitted by Felipe neves de Albuquerque, from Programa de Pós-Graduação em Ciências Médicas da Faculdade de Ciências Médicas da Universidade do Estado do Rio de Janeiro (FCM-UERJ)

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Pedro Ernesto under the protocol number CAAE: 0176.0.228-000-09. 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.

References

1. Brasil. Ministério da Saúde. [Internet]. DATASUS. Informações de saúde, epidemiológicas e mortalidade [acesso13 mar. 2019]. Disponível em: http://datasus.saude.gov.br.
2. Luo N, Fonarow GC, Lippmann SJ, Mi X, Heidenreich PA, Yancy CW, et al. Early adoption of sacubitril/valsartan for patients with heart failure with reduced ejection fraction: insights from get with the Guidelines-Heart Failure (GWTG-HF). JACC Heart Fail. 2017;5(4):305-9.
3. Small KM, Wagoner LE, Levin AM, Kardia S, Liggett SB. Synergistic polymorphisms of beta1- and alpha2C-adrenergic receptors and the risk of congestive heart failure. N Engl J Med. 2002;347(15):1135-42.
4. Abuzaanona A, Lanfear D. Pharmacogenomics of the natriuretic peptide system in heart failure. Curr Hear Fail Rep. 2017;14(6):536-42.
5. Albuquerque FN, Brandão AA, Silva DA, Mourilhe-Rocha R, Duque GS, Gondar AF, et al. Angiotensin-converting enzyme genetic polymorphism: its impact on cardiac remodeling. Arq Bras Cardiol. 2014;102(1):70-9.
6. Luzum JA, English JD, Ahmad US, Sun JW, Canan BD, Sadee W, et al. Association of genetic polymorphisms in the beta-1 adrenergic receptor with recovery of left ventricular ejection fraction in patients with heart failure. J Cardiovasc Transl Res. 2019;12(4):280-9.
7. Borjesson M, Magnusson Y, Hjalmarson A, Andersson B. A novel polymorphism in the gene coding for the beta(1)-adrenergic receptor associated with survival in patients with heart failure. Eur Heart J. 2000;21(22):1853-8.
8. Levin MC, Marullo S, Muntaner O, Andersson B, Magnusson Y. The myocardium-protective Gly-49 variant of the β1-adrenergic receptor exhibits constitutive activity and increased desensitization and down-regulation. J Biol Chem. 2002;277(34):30429-35.
9. Liu WN, Fu KL, Gao HY, Shang YY, Wang ZH, Jiang GH, et al. β1 adrenergic receptor polymorphisms and heart failure: a meta-analysis on susceptibility, response to β-blocker therapy and prognosis. Plos One. 2012;7(7):e37659.
10. Biolo A, Clausell N, Santos KG, Salvaro R, Ashton-Prolla P, Borges A, et al. Impact of β1-adrenergic receptor polymorphisms on susceptibility to heart failure, arrhythmogenesis, prognosis, and response to beta-blocker therapy. Am J Cardiol. 2008;102(6):726-32.
11. Mialet-Perez J, Rathz DA, Petrashevskaya NN, Hahn HS, Wagoner LE, Schwartz A, et al. Beta 1-adrenergic receptor polymorphisms confer differential function and predisposition to heart failure. Nat Med. 2003;9(10):1300-5.
12. Lanfear DE, Peterson EL, Zeld N, Wells K, Sabbah HN, Williams K. Beta blocker survival benefit in heart failure is associated with ADRB1 Ser49Gly genotype. J Card Fail. 2015;21(8):S50.

13. Wang L, Lu L, Zhang F, Chen Q, Shen W. Polymorphisms of β-adrenoceptor and natriuretic peptide receptor genes influence the susceptibility to and the severity of idiopathic dilated cardiomyopathy in a Chinese cohort. J Card Fail. 2010;16(1):36-44.

14. Fiuzat M, Neely ML, Starr AZ, Kraus WE, Felker MG, Donahue M, et al. Association between adrenergic receptor genotypes and beta-blocker dose in heart failure patients: analysis from the HF-ACTION DNA substudy. Eur J Heart Fail. 2013;15(3):258-66.

15. Liggett SB, Mialet-Perez J, Thaneemit-Chen S, Weber SA, Greene SM, Hodne D, et al. A polymorphism within a conserved beta(1)-adrenergic receptor motif alters cardiac function and beta-blocker response in human heart failure. Proc National Acad Sci USA. 2006;103(30):11288-93.

16. Pereira SB, Velloso MW, Chermont S, Quintão MM, Nunes Abdhala R, Giro C, et al. β-adrenergic receptor polymorphisms in susceptibility, response to treatment and prognosis in heart failure: implication of ethnicity. Mol Med Rep. 2013;7(1):259-65.

17. Magnusson Y, Levin MC, Eggertsen R, Nyström E, Mobini R, Schaufelberger M, et al. Ser49Gly of beta1-adrenergic receptor is associated with effective beta-blocker dose in dilated cardiomyopathy. Clin Pharmacol Ther. 2005;78(3):221-31.

18. Mangini S, Silveira F, Silva C, Grativvol P, da Seguro L, Ferreira S, et al. Decompensated heart failure in the emergency department of acardiology hospital. Arq Bras Cardiol. 2008;90(6):400-6.

19. Maqbool A, Hall AS, Ball SG, Balmforth AJ. Common polymorphisms of β1-adrenoceptor: identification and rapid screening assay. Lancet.1999;353(9156):897.

20. Salanti G, Amountza G, Ntzani EE, Ioannidis JP. Hardy–Weinberg equilibrium in genetic association studies: an empirical evaluation of reporting, deviations, and power. Eur J Hum Genet. 2005;13(7):840-8.

21. Raphael C, Briscoe C, Davies J, Ian Whinnett Z, Manisty C, Sutton R, et al. Limitations of the New York Heart Association functional classification system and self-reported walking distances in chronic heart failure. Heart. 2007;93(4):476-82.

22. Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Køber L, Squire IB, et al. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. Eur Heart J. 2013;34(19):1404-13.

23. Leineweber K, Frey UH, Tenderich G, Toliat MR, Zittermann A, Nürnberg P, et al. The Arg16Gly-β(2)-adrenoceptor single nucleotide polymorphism: exercise capacity and survival in patients with end-stage heart failure. Naunyn Schmiedebergs Arch Pharmacol. 2010;382(4):357-65.

24. Forleo C, Resta N, Sorrentino S, Guida P, Manghisi A, Luca V, et al. Association of beta-adrenergic receptor polymorphisms and progression to heart failure in patients with idiopathic dilated cardiomyopathy. Am J Med. 2004;117(7):451-8.

25. Taylor AL. The African American Heart Failure Trial: a clinical trial update. Am J Cardiol. 2005;96(7B):44-8.

26. McNamara DM, Tam SW, Sabolinski ML, Tobelmann P, Janosko K, Venkitachalam L, et al. Endothelial nitric oxide synthase (NOS3) polymorphisms in African Americans with heart failure: results from the A-HeFT trial. J Card Fail. 2009;15(3):191-8.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Short Editorial: Ser49Gly Beta1-adrenergic Receptor Genetic Polymorphism as a Death Predictor in Brazilian Patients with Heart Failure

Antonio Carlos Pereira-Barretto[1,2,3]

Departamento de Cardiopneumologia da FMUSP,[1] *São Paulo, SP – Brazil*
Instituto do Coração (InCor) do HCFMUSP - Serviço de Prevenção e Reabilitação,[2] *São Paulo, SP – Brazil*
Hospital Santa Marcelina – Cardiologia,[3] *São Paulo, SP – Brazil*

Short Editorial: Ser49Gly Beta1-adrenergic Receptor Genetic Polymorphism as a Death Predictor in Brazilian Patients with Heart Failure

Heart failure (HF) is a disease that develops into high morbidity/mortality. However, not all patients have a bad evolution. Symptomatic patients and those who require hospitalization for treatment comprise the group with the worst prognosis. Symptom intensity has shown to be a good predictor of prognosis. However, in less symptomatic patients, we have a much more limited capacity to identify those who will have a worse evolution.[1]

In the article "Ser49Gly Beta1-adrenergic Receptor Genetic Polymorphism as a Death Predictor in Brazilian Patients with Heart Failure", published in this issue, the authors discuss a current topic, in which they show that patient evolution is, at least in part, related to their genetic profile, and that this profile determines the intensity of HF and symptom development.[2]

Neurohormonal stimulation has an important pathophysiological role in HF, and multicentric clinical trials have fully documented that the blockade of the overactivated renin-angiotensin-aldosterone and sympathetic systems modifies the disease evolution. And in this context, the role of the sympathetic nervous system is well established and possibly has the role of the greatest villain in the history of HF. The response to neurohormonal stimulation is not the same in all patients and the genetic polymorphism influences this response.

The sympathetic activity is mediated by type 1 and type 2 beta-adrenergic receptors.[3] The genetic polymorphism of these receptors has been evaluated and the sympathetic activity differs according to the polymorphism. For the beta-1 receptor, two polymorphisms have been more frequently studied: Ser19Gly and Arg389Gly and for the beta-2receptor, also two polymorphisms: Gly16Arg and Gln27Glu.[3]

The beta-1 receptor polymorphism has been shown to play a role in the incidence of HF, response to beta-blockers, echocardiographic outcomes, functional capacity, incidence of cardiac arrhythmia and the clinical evolution of patients.[2,3] However, most studies were carried out with small populations and the outcomes have not shown homogeneous results, although it has been possible to verify that the genetic constitution determines patient evolution, including treatment response.

One can verify this fact, in relation to the beta-2 receptor polymorphism, in the FAST-Carvedilol study. When assessing survival, one can document that by analyzing patients considering the polymorphism, evaluating the DD-ID and II genotypes, the carriers of the polymorphism II had higher mortality than the DD and ID variants. However, the most interesting result was that patients II, when they received an optimized dose of carvedilol (> 50% of the target dose), showed a significant reduction in mortality, while in patients with the DD and ID variants, the dose did not change the evolution.[4] As the study result, we observed that group II treated with a low dose of carvedilol had a 6-fold greater chance of dying than the group that received an optimized dose of carvedilol.[4]

In the same line of research, in the MERIT-HF study, when analyzing the Beta-1 receptor polymorphism, it was observed that there were patients receiving high doses of beta-blockers who did not respond to treatment, whereas others showed significant improvement.[3] In the BEST study, the genetic polymorphism was associated to the lack of response to the beta-blocker bucindolol. This was one of the few multicenter studies with a significant number of patients that prospectively analyzed the role of the polymorphism in the therapeutic response to a beta-blocker. The polymorphism was analyzed in this multicenter trial with more than 1,000 patients and showed that patients with the wild beta-1 receptor Gly389 polymorphism did not respond to treatment with bucindolol. On the other hand, those without this polymorphism had reduced mortality with bucindolol.[3] The researchers consider that the data on the polymorphism are not always consistent and that at the moment it is better not to use this tool to guide treatment.[2]

However, its role in the evolution of HF patients continues to supply us with information, allowing a better understanding of this complex syndrome. The studies have shown that the adrenergic system response mediated by the genetic variants of central or peripheral adrenoceptors has a role in the physiology of HF. As already shown, this inter-individual variability even changes the prognosis of HF, with some patients showing more cardiac events despite the moderate

Keywords

Heart Failure/physiopathology; Heart Failure/mortality; Prognosis; Genetic,Polymorphism; Sympathetic Nervous System; Adrenergic beta-1; Receptor Agonists; Adrenergic beta-2; Receptor Agonists.

Mailing Address: Antonio Carlos Pereira-Barretto •
Instituto do Coração, Hospital das Clinicas da Faculdade de Medicina da Universidade de São Paulo, Av Éneas de Carvalho Aguiar 44, Cerqueira Cesar, Postal Code 05403-000, São Paulo - Brazil
E-mail: pereira.barretto@incor.usp.br

DOI: https://doi.org/10.36660/abc.20200183

clinical stability of ventricular dysfunction and preserved exercise capacity. Conversely, others, clinically classified as having advanced HF, evolve with a prolonged and unexpected survival. Moreover, the data showed that part of the perceived differences in the effectiveness of beta-blockers, as well as the variability of responses to the latter can be attributed to some genetic variations that affect beta receptors and their signaling pathways.[2,3]

In Brazil, the beta-1 receptor polymorphism has been studied in Rio de Janeiro and Rio Grande do Sul.[2,5]

In the study discussed in this short editorial, the authors emphasize that the cardiac beta-1 adrenergic receptor (Rβ1) is the main structure responsible for mediating the effects of adrenaline and that the sustained stimulation of this system results in multiple deleterious effects, especially cardiotoxicity. Genetic variants are associated with different activities of this receptor. The authors studied the genetic polymorphism identified at position 145 of the nucleotide, in which serine is replaced by glycine at position 49 (Rβ1-Ser49Gly).[2]

This study describes, in a Brazilian population, the association between the genotypes of the Ser49Gly Beta1-adrenergic Receptor Genetic Polymorphism and the clinical evolution in 178 patients with HF, with a mean follow-up of 6.7 years.[2] This is a study with Ser49Gly genotyping in the context of HF with the longest follow-up time ever published. Its main finding was the association of the Gly-Gly genetic polymorphism with a protective effect for clinical outcomes, with better clinical evolution assessed by NYHA functional class and lower risk of death. The longer follow-up allowed us to better assess the HF evolution aspects and to verify that the Gly allele is associated with better clinical evolution; however, there was a potential influence of ethnicity on these genotypes, reversing this benign behavior in some populations. An important point was to allow the assessment of prognosis in little symptomatic patients, increasing the accuracy of the prognostic evaluation for these patients, as well.

As for the prognosis, the results of this study were similar to those obtained in the study carried out in Rio Grande do Sul,[5] adding an important contribution by identifying that patients with the Gly-Gly profile, which is less frequent, remained little symptomatic throughout the follow-up, thus identifying a group of patients with lower evolution potential.[3]

However, it should be noted that the assessed sample is small and confirmatory studies are necessary to verify this hypothesis, aiming to show whether the genetic variants of beta-adrenergic receptors can help to identify patients with HF who will have a lower disease progression and whether they will be more responsive to beta-blockers and, as a consequence, have a better clinical evolution.

The results allow us to suppose that, in the future, before starting a treatment with neurohormonal blockers or beta-blockers, the genetic profile will be identified, and medications will be prescribed only to those who are responsive to them.

References

1. Comitê Coordenador da Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda, Rohde LEP, Montera MW, Bocchi EA, Clausell NO, Albuquerque DC; Sociedade Brasileira de Cardiologia.. Arq Bras Cardiol. 2018;111(3):436-539.
2. Shin J, Johnson JA. Beta-blocker pharmocogenetics in heart failure. Heart Fail Rev. 2010;15(3):187-96.
3. Albuquerque FN, Brandão AA, Silva DA e cols. Ser49Gly Beta1-adrenergic Receptor genetic Polymorphism as a Death Predictor in Brazilian Patients with Heart Failure. Arq Bras Cardiol. 2020; 114(4):616-624.
4. Melo DSB, Pereira-Barretto AC, Cardoso JN, Oliveira AI, Ochiai ME, Melo FSA, et al. Polimorfismos genéticos como preditores prognósticos em pacientes com insuficiência cardíaca avançada após rápida titulação com betabloqueadores. In: 11 Congresso Brasileiro de Insufiiência Cardíaca. Recife (PE);2012. Arq Bras Cardiol. 2012;99(2 supl 2):1-148.
5. Biolo A, Clausell N, Santos KG, Salvaro R, Ashton-Prolla P, Borges A, et al. Impact ofβ1-adrenergic receptor polymorphisms on susceptibility to heart failure, arrhythmogenesis, prognosis, and response to beta-blocker therapy. Am J Cardiol. 2008;102(6):726-32.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Original Article

Extent of Left Atrial Ablation Lesions and Atrial Fibrillation Recurrence after Catheter Ablation – A Systematic Review and Meta-Analysis

Eduardo Thadeu de Oliveira Correia,[1] *Letícia Mara dos Santos Barbetta,*[1] *Evandro Tinoco Mesquita*[1]

Hospital Universitário Antonio Pedro,[1] *Niterói, RJ – Brazil*

Abstract

Background: Atrial fibrillation (AF) is known to induce atrial remodeling, which promotes fibrosis related to arrhythmogenesis. Accordingly, since scars induced by catheter ablation (CA) can reduce unablated fibrotic areas, greater extent of left atrial (LA) scarring may be associated with less AF recurrence after CA.

Objectives: This study aims to investigate, through systematic review and meta-analysis, whether the amount of LA scarring, seen on late gadolinium enhancement magnetic resonance imaging, is associated with less AF recurrence after CA.

Methods: The recommendations of the MOOSE guideline were followed. Database search was conducted in PubMed and Cochrane Central Register of Controlled Trials (comentário 1) until January 2019 (comentário 2). Two authors performed screening, data extraction, and quality evaluation. All studies were graded as good quality. A funnel plot was generated, showing no publication bias. Statistical significance was defined as p value < 0.05.

Results: Eight observational studies were included in the systematic review, four of which were included in the meta-analysis. Six of the eight studies included in the systematic review showed that greater extension of LA scarring is associated with less AF recurrence after CA. Meta-analysis showed that greater extension of LA scarring is associated with less AF recurrence (SMD = 0.52; 95% CI 0.27 – 0.76; p < 0.0001).

Conclusion: Greater extension of LA scarring is possibly associated with less AF recurrence after CA. Randomized studies that explore ablation methods based on this association are fundamental. (Arq Bras Cardiol. 2020; 114(4):627-635)

Keywords: Atrial Fibrillation; Catheter Ablation; Heart Atria/injuries; Meta-Analysis as Topic; Databases,Bibliographic.

Introduction

Radiofrequency catheter ablation (RFCA) is a standard procedure for correction of atrial fibrillation (AF) in patients who have not responded to previous antiarrhythmic drug therapies.[1] However, this procedure is related to high AF recurrence rates, even in the best hands.[2] Accordingly, electrophysiologists and interventional cardiologists are seeking techniques that aim to reduce AF recurrence.

AF is known to induce atrial remodelling, increasing the amount of fibrotic tissue in the myocardium, which can promote atrial arrhythmogenesis, reinforcing the vicious cycle of AF.[3-5] In this manner, since the scars induced by catheter ablation (CA) can reduce unablated fibrotic areas, the extent of the left atrial (LA) scars could be associated with less AF recurrence after CA. However, there are currently no systematic reviews or meta-analyses that have investigated this relationship, although they are the highest quality of evidence available.

Mailing Address: Eduardo Thadeu de Oliveira Correia •
Hospital Universitário Antonio Pedro - Avenida Marquês do Paraná, 303. Postal Code 24033-900, Centro, Niterói, RJ – Brazil
E-mail: etocorreia@outlook.com
Mansucript received November 26, 2018, revised manuscript April 29, 2019, accepted June 05, 2019

DOI: https://doi.org/10.36660/abc.20180378

Accordingly, this systematic review and meta-analysis aims to investigate if the amount of LA scarring, visualized by late gadolinium-enhanced magnetic resonance imaging (LGE-MRI), could be associated with less AF recurrence after CA, which can provide a solid background for designing new ablation strategies that improve patient outcomes.

Methods

A systematic review was performed according to the criteria established by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group.[6]

Search strategies

Two investigators (ETOC and ETM) searched the PubMed and Cochrane Central Register of Controlled Trials, until January 2019. The search strategy comprised a combination of English terms and Medical Subject Headings (MeSH) descriptors, consisting of nine keywords [(left atrial OR left atrium) AND (scar OR scarring OR remodelling OR fibrosis OR enhancement) AND (ablation OR pulmonary vein isolation)]. A manual search of references was also used to identify possible studies for inclusion. Each title and abstract were independently analyzed by both investigators, who selected the articles which were relevant to the review. Subsequently, the full texts of the remaining articles were reviewed to select which

would be included for qualitative or quantitative analysis. In the event of disagreement, the authors reached a decision through discussion and consensus.

Inclusion criteria for qualitative analysis

We included observational studies (with prospective or retrospective design) in humans, whose objective was to study the association between post-ablation LA scarring and AF recurrence after CA.

Studies that met the following criteria were included: 1) The study evaluated AF or total arrhythmia recurrence after CA in human subjects; 2) The publication was an original study; 3) The mean follow-up period was equal to or longer than 3 months; 4) The study included more than 20 subjects; 5) The study evaluated LA scarring by LGE-MRI after CA.

Inclusion criteria for quantitative analysis

Meta-analysis included studies that met the previous qualitative analysis criteria and reported means and 95% confidence intervals (CI) of total LA scarring in patients with and without AF recurrence after CA.

Quality assessment

Risk of bias in the studies was evaluated by the National Heart, Lung and Blood Institute Quality Assessment Tool for Case Series Studies.[7] Evaluation was independently conducted by two raters (ETOC and LMSB), and, in the event of disagreement, the raters reached a decision by consensus. The following characteristics were assessed: 1) Was the study question or objective clearly stated? 2) Was the study population clearly and fully described, including a case definition? 3) Were the cases consecutive? 4) Were the subjects comparable? 5) Was the intervention clearly described? 6) Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants? 7) Was the length of follow-up adequate? 8) Were the statistical methods well-described? 9) Were the results well described?

Following assessment of those characteristics, the authors assigned a quality rating (good, fair, or poor) to each of the studies. Studies were rated as 'poor' if they met fewer than three criteria; 'fair' if they met three to five criteria; and 'good' if they met more than five criteria. All studies selected met almost all of the criteria and received a good quality rating from both raters. Quality assessment of the included studies is reported in Table 1.

Data extraction

Using a standard data extraction form, two researchers (ETOC and LMSB) performed data extraction, which was cross-verified by a third researcher (ETM). Extracted data included the following: 1) First author's last name and publication year; 2) Characteristics of included studies: number of patients, study region, study design, ablation strategy, measurement method of LA scarring, method of AF detection, length of follow-up period, and main findings; 3) Outcome results: means and 95% CI of total LA scarring in patients with and without AF recurrence after CA.

Statistical analysis

The association between AF recurrence and total LA scarring following RFCA was measured by standardized mean difference (SMD) with 95% CI, and standard errors were determined using the corresponding 95% CI. The inverse variance method was used to weigh studies for combined statistical analysis. Statistical significance was defined as p value < 0.05. Heterogeneity between studies was assessed using Cochran's Q test and I^2 statistics and subsequently evaluated by I^2 values. I^2 values below 30% were defined as low heterogeneity; values between 30% and 60% were considered moderate heterogeneity; and values above 60% were considered high heterogeneity.[8] The fixed-effects model was chosen due to the small number of studies included and the low heterogeneity. Meta-regression was not carried out due to the small number of studies included. The results are reported in a forest plot with 95% CI. Publication bias was verified using a funnel plot. All analyses were conducted using Review Manager 5.3 software.

Results

Study selection

Initially, a total of 790 studies were identified by the database search, 695 in PubMed and 95 in the Cochrane Central Register of Controlled Trials. Duplicate analysis revealed 28 duplicates, which were subsequently eliminated. After careful reading of the title and abstract, 742 of the 762 studies were excluded, because they were not related to the present review. Twenty studies were analyzed in full text, twelve of which were excluded, because they were not related to the present review. Finally, eight studies[9-16] were included in the qualitative analysis, and four were included in the meta-analysis.[9-11,15] The study selection flow diagram is shown in Figure 1.

Characteristics of the included studies

Eight studies were included in this review,[9-16] comprising six prospective single center observational studies and two prospective multicenter studies (Table 1). The systematic review included a total of 703 patients, and meta-analysis included 295. The follow-up period ranged from 3 to 12 months. All studies used LGE-MRI to identify post-CA LA scarring. Pulmonary vein isolation (PVI) was the ablation strategy in all of the studies. The studies by Akoum et al.[14] and Hunter et al.[16] used both catheter and cryoballoon ablation. Table 1 and Table 2 summarize the characteristics of all included studies.

Total LA scarring post-ablation and AF recurrence

Six of the eight included studies[8-12,14] found that the extent of LA scarring was associated with less AF recurrence after CA.

In the study by Hunter et al.,[16] there was no significant association between identification of ablation lesions and freedom from AF (53% with ablation lesions identified remained free from AF vs. 65% in those with no lesions

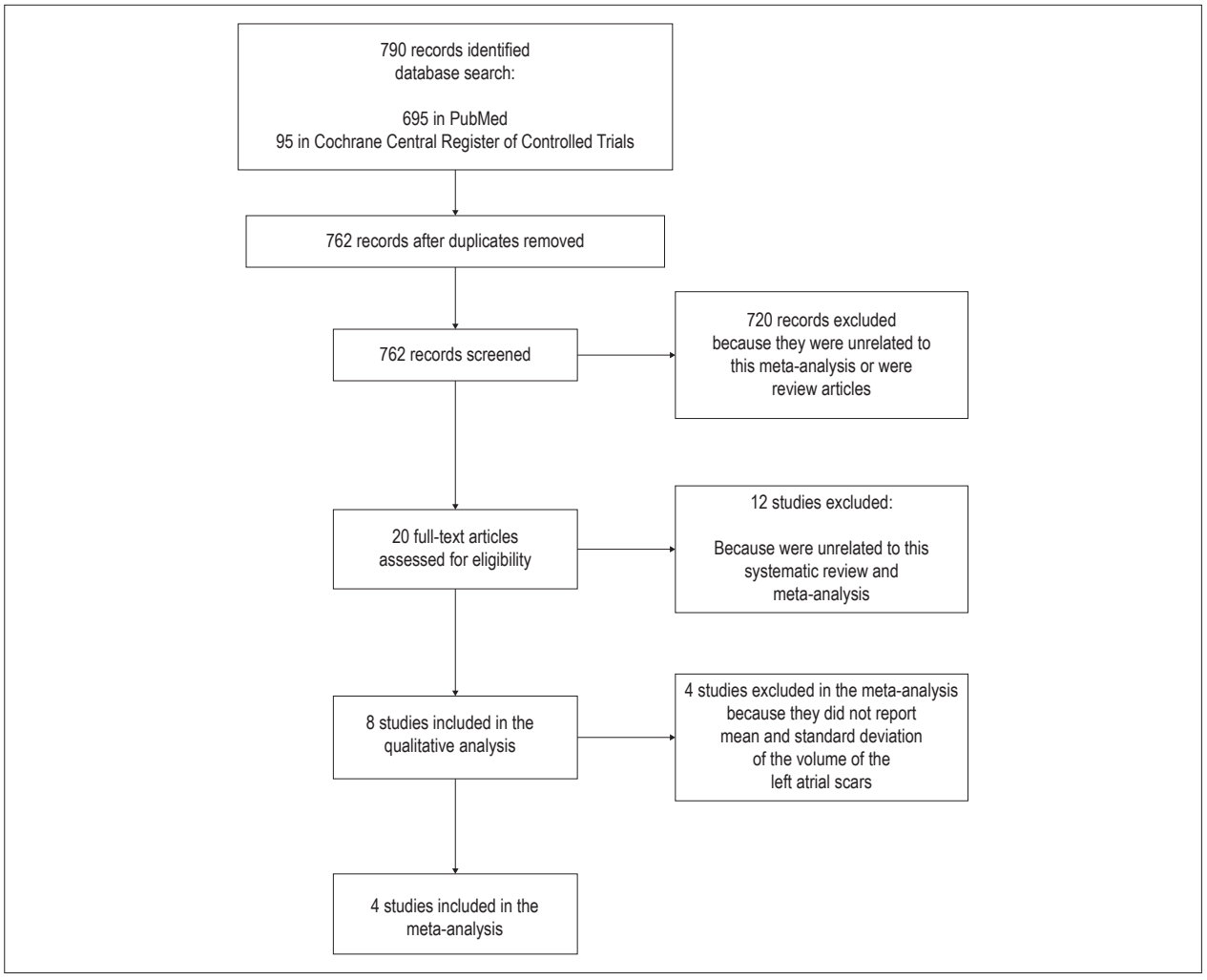


Figure 1 – *Study selection flow diagram.*

identified, p = 0.560). The study also performed binary logistic regression, which confirmed that there was no significant association between identification of ablation lesions and freedom from AF.[16]

The 2015 study by Akoum et al.[14] found that ablation-induced scarring was not a statistically significant predictor of less AF recurrence (hazard ratio = 0.95; p = 0.097). However, according to this same study, when performing scar homogenization, inducing ablation lesions in prior fibrotic tissue leads to a lower recurrence rate, because less heterogeneous fibrotic tissue remains.[14]

Meta-analysis

The present meta-analysis shows that total LA scarring post-ablation is associated with less AF recurrence after CA (SMD = 0.52, 95% CI 0.27 – 0.76, p < 0.0001), as shown in Figure 2. The heterogeneity test showed that there were no significant differences between studies (p = 0.4, I^2 = 0%). A funnel plot (Figure 3) was used to verify the existence of publication bias. There was no obvious asymmetry, suggesting that there was no publication bias.

Discussion

The importance of CA for AF correction has grown since its introduction. A recent meta-analysis by Kheiri et al. that included seven randomized controlled trials showed that CA was associated with better outcomes in patients with AF and heart failure, in comparison with medical treatment.[17] Therefore, interventional cardiologists should seek ablation strategies that reduce AF recurrence and procedural risks. This systematic review and meta-analysis shows that the extent of LA scarring after ablation is possibly associated with less AF recurrence after CA, paving the way for future research on ablation methods with lower chances of post-procedural recurrence.

Substrate modification

Previous studies in animal models have established the concept that "AF begets AF" by atrial remodeling.[18] In this manner, AF stimulates atrial fibrotic alterations that maintain and increase the AF burden, leading to a vicious cycle.[19] Furthermore, in spite of some limitations, studies in humans have shown that patients with paroxysmal AF have increased LA stiffness, possibly due to an increase in LA fibrosis.[20,21]

Table 1 – Characteristics of the included studies and quality evaluation

Study, year	Region	Type of Study	N	Paroxysmal, N (%)	AF detection method	Follow up	Quality	p threshold
McGann et al., 2008[9]	North America	Single center, prospective, observational	46	22 (48%)	Patient reports, event monitoring, Holter monitoring, and ECG data.	3 months	Good	0.05
Peters et al., 2009[10]	North America	Single center, prospective, observational	35	19 (54%)	7-day event monitor at multiple intervals	6.7 ± 3.6 months	Good	0.05
Badger et al., 2010[11]	North America	Single center, prospective, observational	144	57 (40%)	8-day Holter monitoring and ECG at 3 months, 6 months, and 1 year	10.23 ± 5.14 months (range, 6 to 20 months)	Good	0.05
Akoum et al., 2011[12]	North America	Single center, prospective, observational	120	50 (42%)	12-lead ECG and 8-day Holter monitor at 3 months after ablation and in 3-month intervals thereafter. Additional ECG were obtained when patients reported symptoms.	283 ± 167 days	Good	0.05
McGann et al., 2011[13]	North America	Single center, prospective, observational	37	NR	NR	1 year	Good	0.05
Hunter et al., 2013[16]	Europe	Multicenter, prospective, observational	50	50 (100%)	7 days of ambulatory ECG monitoring at 3 and 6 months	6 months	Good	0.05
Akoum et al., 2015 [14]	North America, Europe, and Oceania	Multicenter, prospective, observational	177	116 (66%)	ECG or ambulatory monitor recordings	At least 1 year	Good	0.05
Parmar et al., 2015 [15]	North America	Single center, prospective, observational	94	45 (48%)	12-lead ECG and 30-day event monitor at 3 and 6 months and 1 year, and every 6 months thereafter. Patients who experienced symptoms were given additional ECG and Holter monitors	Mean follow up of 336 days	Good	0.05

AF: atrial fibrillation; ECG: electrocardiogram; LA: left atrium; LGE-MRI: Late gadolinium enhanced magnetic resonance imaging; NR: not reported.

In addition to that, animal studies have demonstrated that 80% of AF triggers are located in the posterior wall, including the pulmonary vein (PV) region.[22] A previous meta-analysis has shown that isolation of a part of the posterior LA reduces the recurrence of AF after CA.[23] Therefore, an increase in the extent of LA ablation may promote greater substrate modification, decreasing the amount of viable LA tissue capable of harboring AF by overlapping PV and non-PV triggers with ablation lesions.

PV scarring

The clinical application of real-time MRI may make it possible to visualize LA scarring during the procedure, making it easier to induce scarring.[24] However, as real-time MRI is still a new and expensive imaging method, alternatives such as driver-guided CA by electroanatomic mapping to visualize LA scars might be an option for optimizing outcomes. A recent meta-analysis by Ramirez et al.[25] reported an association between driver-guided CA for AF and increased freedom from AF, in comparison with conventional strategies. However, this meta-analysis included primarily nonrandomized studies of moderate quality. Future observational studies can help build evidence to prove whether electroanatomic mapping can assist in creating contiguous scar lesions around the PV.

Risks of targeting more LA scarring

Even though this meta-analysis shows that more extensive ablation reduces the risk of AF recurrence, this strategy is not risk free, given that the procedure may decrease LA compliance, LA volume, and LA systolic function, which may induce the development of the stiff left atrial syndrome (SLAS).[26] SLAS, which was described in 1988 by Pilote et al.,[27] is characterized by a decline in LA diastolic function and pulmonary hypertension.[28] Although this may represent a severe consequence of RFCA, in a case series study by Gibson et al., the condition was reported in only 1.4% of patients who underwent RFCA.[28]

Furthermore, previous studies found that LA scar volume after CA was associated with depressed LA systolic function.[26,29] Ablation scars in the posterior LA wall, however, had less effect on LA systolic function.[26]

Another risk of CA that extensive ablation may increase is the possibility of esophageal injury due to the anatomical relationship between the esophagus and the posterior LA wall.[29] The esophagus is separated from the posterior LA by a thin layer of fat, being prone to injury during AF ablation.[30] Possible esophageal injuries include perforation, atrio-esophageal fistula formation, and peri-esophageal nerve injury.[30] To minimize the potential risks of esophageal

Table 2 – Characteristics of the included studies and main findings

Study, year	Ablation method	Ablation strategy	Catheter used	Time of LGE-MRI	Main Findings
McGann et al., 2008[9]	RFCA	PVI in addition to LA posterior wall and septal debulking.	Externally irrigated ablation catheter	3 months after ablation	Patients with scar ratios > 13% are 18.5 times more likely to have a favorable outcome and freedom from AF at 3 months
Peters et al., 2009[10]	RFCA	PVI without routine addition of empiric ablation lines in the LA.	8-mm standard tip: N = 29 (83%); 3.5-mm externally irrigated tip ablation catheter: N = 6 (17%)	46 ± 28 days after ablation	AF recurrence during the first year is associated with a lesser degree of PV and LA scarring after ablation
Badger et al., 2010[11]	RFCA	PVA isolation with posterior wall and septal debulking	3.5-mm Thermocool irrigated tip ablation catheter	3 months after ablation	Patients with successful AF termination had higher average total LA wall scar after ablation of 16.4 ± 9.8% (p = 0.004) and percent PVA scar of 66.2 ± 25.4 (p = 0.01)
Akoum et al., 2011[12]	RFCA	PVI in a circular fashion in the PVA and additional debulking in LA posterior wall and septum	10-pole circular mapping catheter: N = NR; 3.5 mm Thermocool ablation catheter: N = NR	3 months after ablation	Overall post-ablation LA wall scarring predicts recurrence in moderate fibrosis stages
McGann et al., 2011[13]	RFCA	PVI in addition to posterior wall and septal debulking	3.5-mm Thermocool ablation catheter	Immediately following ablation and 3 months after ablation	At 1-year follow-up, patients with moderate scar formation 3 months after ablation had no AF recurrence. In comparison, all recurrences occurred in patients with mild scar formation 3 months after ablation (p = 0.02).
Hunter et al., 2013[16]	RFCA and cryoballoon ablation	PVI by WACA or ostial ablation with a cryoballoon	3.5-mm irrigated ablation catheter: N = NR For cryoballoon ablation an 11F FlexCath sheath delivered a 23- or 28-mm cryoablation balloon: N = NR	Pre-ablation and 3 months after ablation	The proportion of patients free from AF was unaffected by whether ablation lesions could be identified on imaging: 16 of 30 patients (53%) with ablation lesions identified remained free from AF compared to 13 of 20 patients (65%) with no lesions identified (p = 0.560).
Akoum et al., 2015[14]	RFCA and cryoballoon ablation	PVI with CFAE ablation, linear ablation lines of the CTI, and other ablations in the LA (roof line, mitral isthmus line, posterior wall)	Cryo-balloon: N = 12 (6.7 %); Multi-electrode duty-cycled phased radiofrequency ablation: N = 8 (4.5 %); Nonirrigated and open-irrigation radiofrequency catheters: N = 157 (88.7 %)	3 months after ablation	The more scarring overlaps fibrosis, the better the arrhythmia-free survival
Parmar et al., 2015[15]	RFCA	PVI and additional debulking of the LA posterior wall	3.5-mm ablation catheter	3 months after ablation	Poor scar formation on LGE-MRI was associated with higher rates of AF recurrence

AF: atrial fibrillation; CFAE: complex fractionated atrial electrogram; CTI: cavotricuspid isthmus; LA: left atrium; LGE-MRI: Late gadolinium enhanced magnetic resonance imaging; NR: not reported; PV: pulmonary vein; PVA: pulmonary vein antrum; PVI: pulmonary vein isolation; RFCA: radiofrequency catheter ablation; WACA: wide area circumferential radiofrequency ablation

injuries, strategies, such as reducing power in the posterior LA wall, monitoring temperature in the esophagus, irrigating the esophagus with cold water, and pre-procedural imaging, should be adopted.[31-33]

Reproducibility

A previous study by Chubb et al.,[34] which investigated post-ablation atrial scar, using LGE-MRI, in 40 subjects undergoing first time ablation for AF, showed that post-ablation visualization of induced scars in the LA is reproducible. Moreover, they concluded that imaging should be performed at least 20 minutes after administration of gadolinium-based contrast for better reproducibility.[34] However, the study by Hunter et al. analyzed in the present review, which included 50 patients, concluded that LGE imaging of atrial scar is not yet sufficiently accurate to identify ablation lesions or determine lesion distribution reliably. A published consensus by the European Heart Rhythm Association stated that there is still neither recommendation nor expert consensus on the role of LGE-MRI to assist AF ablation procedures. The consensus, nevertheless, states that the available data are intriguing enough to warrant further research.[35]

STAR AF II and DECAAF II

Although previous studies have demonstrated the positive impact of targeting ablation strategies beyond circumferential pulmonary vein isolation (CPVI), the STAR AF II trial showed a different scenario.[23,36] The STAR AF II was a randomized

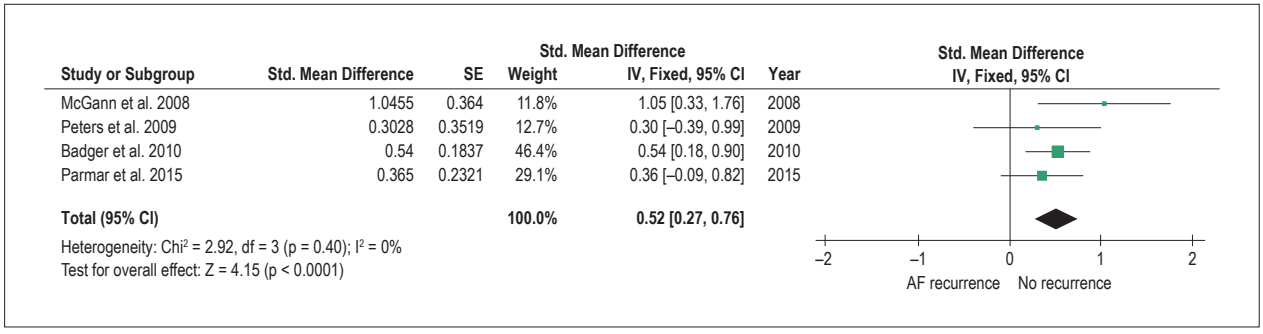


Figure 2 – *Forest plot showing that the extent of left atrial scarring is associated with less atrial fibrillation recurrence after catheter ablation. CI: confidence interval; IV: inverse variance*

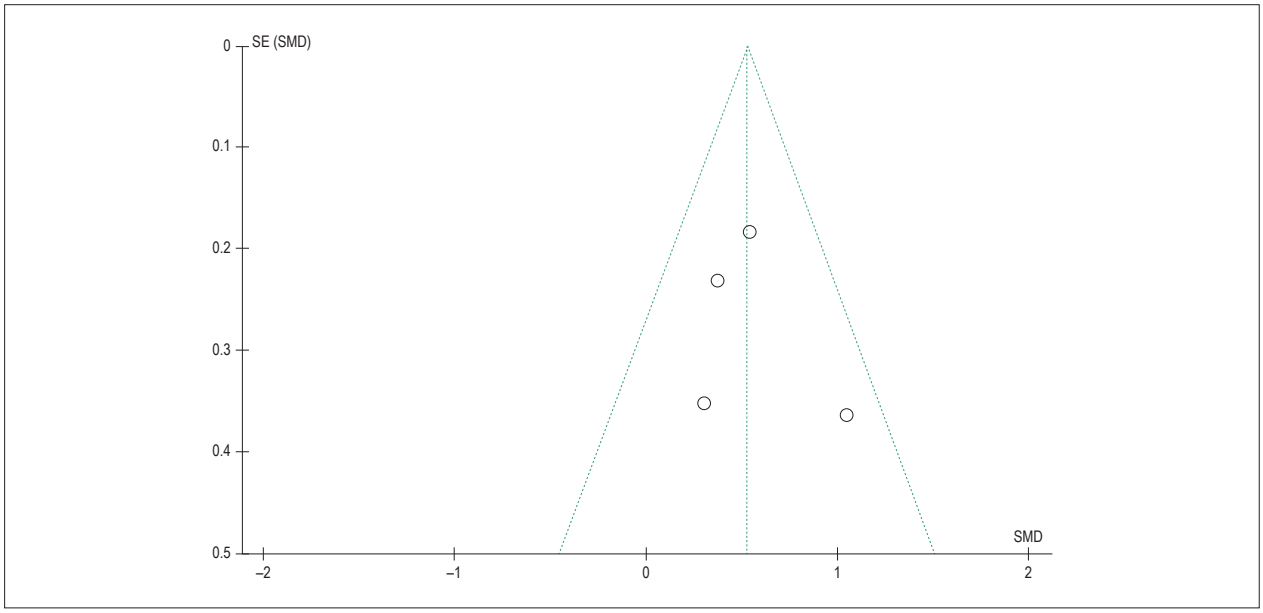


Figure 3 – *Funnel plot showing no publication bias.*

multicenter study, which, in patients with persistent AF, compared CPVI alone, CPVI plus linear ablation across the LA roof and mitral valve isthmus, and CPVI plus ablation of complex fractionated electrograms. No reduction was found in the recurrence of AF when additional strategies beyond CPVI were performed.[36]

The DECAAF study showed that LA fibrosis visualized by LGE-MRI was a strong predictor of ablation outcome, and the more ablation-induced scarring overlapped fibrotic tissue, the better the outcome.[37] Accordingly, the DECAAF II study will randomize patients with persistent AF to receive either conventional PVI ablation or PVI guided by LGE-MRI.[38]

Future studies

The increased use of CA for AF correction in clinical practice requires better strategies to reduce post procedural failures. It is necessary to conduct randomized controlled trials that compare driver-guided CA by electroanatomic mapping with traditional ablation methods. Moreover, it is important to standardize LGE-MRI to detect LA scars in order to guarantee its reproducibility. In addition to that, developing real-time MRI on a larger scale might reduce its costs, making it possible to use in the future.

Limitations

Although the present systematic review and meta-analysis provides a significant increase in the number of patients analyzed, the number of patients included is limited. Moreover, only four studies were included in the quantitative analysis, and all of them were observational studies. Although LGE-MRI is feasible to detect post-ablation atrial scar, its reproducibility needs to be further studied.

Conclusion

The present review shows that the extent of post-ablation LA scars is possibly associated with less AF recurrence after

CA (SMD = 0.52; 95% CI 0.27 – 0.76; p < 0.0001), which paves the way for scar-guided ablation strategies. However, the reproducibility of this imaging method needs to be further studied and improved. It is necessary to conduct randomized controlled trials, such as the DECAAF II trial, that investigate ablation methods based on this association in order to provide patients with the best treatment option, with minimal risk of AF recurrence and complications.

Author contributions

Conception and design of the research, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Correia ETO, Barbetta LMS, Mesquita ET; Acquisition of data: Correia ETO, Barbetta LMS; Statistical analysis: Correia ETO.

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. Wilber DJ, Pappone C, Neuzil P, De Paola A, Marchlinski F, Natale A, et al. Comparison of antiarrhythmic drug therapy and radiofrequency catheter ablation in patients with paroxysmal atrial fibrillation: a randomized controlled trial. JAMA. 2010;303(4):333-40.
2. Weerasooriya R, Khairy P, Litalien J, Macle L, Hocini M, Sacher F, et al. Catheter ablation for atrial fibrillation: are results maintained at 5 years of follow-up? J Am Coll Cardiol. 2011;57(2):160-6.
3. Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. J Am Coll Cardiol. 2008;51(8):802-9.
4. Nattel S, Harada M. Atrial remodeling and atrial fibrillation: recent advances and translational perspectives. J Am Coll Cardiol. 2014;63(22):2335-45.
5. Allessie MA, Konings K, Kirchhof CJ, Wijffels M. Electrophysiologic mechanisms of perpetuation of atrial fibrillation. Am J Cardiol. 1996;77(3):10A-23A.
6. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. JAMA. 2000;283(15):2008-12.
7. National Heart, Lung, and Blood Institute. Quality Assessment Tool for Case Series Studies [Internet]. Maryland, USA: NIH; 2019 [cited 12 out 2018]. Available from: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools.
8. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58.
9. McGann CJ, Kholmovski EG, Oakes RS, Blauer JJ, Daccarett M, Segerson N, et al. New magnetic resonance imaging-based method for defining the extent of left atrial wall injury after the ablation of atrial fibrillation. J Am Coll Cardiol. 2008;52(15):1263-71.
10. Peters DC, Wylie JV, Hauser TH, Nezafat R, Han Y, Woo JJ, et al. Recurrence of atrial fibrillation correlates with the extent of post-procedural late gadolinium enhancement: a pilot study. JACC Cardiovasc Imaging. 2009;2(3):308-16.
11. Badger TJ, Daccarett M, Akoum NW, Adjei-Poku YA, Burgon NS, Haslam TS, et al. Evaluation of left atrial lesions after initial and repeat atrial fibrillation ablation: lessons learned from delayed-enhancement MRI in repeat ablation procedures. Circ Arrhythm Electrophysiol. 2010;3(3):249-59.
12. Akoum N, Daccarett M, McGann C, Segerson N, Vergara G, Kuppahally S, et al. Atrial fibrosis helps select the appropriate patient and strategy in catheter ablation of atrial fibrillation: a DE-MRI guided approach. J Cardiovasc Electrophysiol. 2011;22(1):16-22.
13. McGann C, Kholmovski E, Blauer J, Vijayakumar S, Haslam T, Cates J, et al. Dark regions of no-reflow on late gadolinium enhancement magnetic resonance imaging result in scar formation after atrial fibrillation ablation. J Am Coll Cardiol. 2011;58(2):177-85.
14. Akoum N, Wilber D, Hindricks G, Jais P, Cates J, Marchlinski F, et al. MRI Assessment of ablation-induced scarring in atrial fibrillation: analysis from the DECAAF study. J Cardiovasc Electrophysiol. 2015;26(5):473-80.
15. Parmar BR, Jarrett TR, Kholmovski EG, Hu N, Parker D, MacLeod RS, et al. Poor scar formation after ablation is associated with atrial fibrillation recurrence. J Interv Card Electrophysiol. 2015;44(3):247-56.
16. Hunter RJ, Jones DA, Boubertakh R, Malcolme-Lawes LC, Kanagaratnam P, Juli CF, et al. Diagnostic accuracy of cardiac magnetic resonance imaging in the detection and characterization of left atrial catheter ablation lesions: a multicenter experience. J Cardiovasc Electrophysiol 2013;24(4):396-403.
17. Kheiri B, Osman M, Abdalla A, Haykal T, Ahmed S, Bachuwa G, et al. Catheter ablation of atrial fibrillation with heart failure: An updated meta-analysis of randomized trials. Int J Cardiol. 2018 Oct 15;269:170-3.
18. Wijffels MC, Kirchhof CJ, Dorland R, Allessie MA. Atrial fibrillation begets atrial fibrillation. A study in awake chronically instrumented goats. Circulation. 1995;92(7):1954-68.
19. Li D, Fareh S, Leung TK, Nattel S. Promotion of atrial fibrillation by heart failure in dogs: atrial remodeling of a different sort. Circulation. 1999;100(1):87-95.
20. Yoon YE, Kim HJ, Kim SA, Kim SH, Park JH, Park KH, et al. Left atrial mechanical function and stiffness in patients with paroxysmal atrial fibrillation. J Cardiovasc Ultrasound. 2012;20(3):140-5.
21. Ágoston G, Szilágyi J, Bencsik G, Tutuianu C, Klausz G, Sághy L, et al. Impaired adaptation to left atrial pressure increase in patients with atrial fibrillation. J Interv Card Electrophysiol. 2015;44(2):113-8.
22. Sánchez-Quintana D, López-Mínguez JR, Pizarro G, Murillo M, Cabrera JA. Triggers and anatomical substrates in the genesis and perpetuation of atrial fibrillation. Curr Cardiol Rev. 2012;8(4):310-26.

23. He X, Zhou Y, Chen Y, Wu L, Huang Y, He J. Left atrial posterior wall isolation reduces the recurrence of atrial fibrillation: a meta-analysis. J Interv Card Electrophysiol. 2016;46(3):267-74.

24. Eitel C, Hindricks G, Grothoff M, Gutberlet M, Sommer P. Catheter ablation guided by real-time MRI. Curr Cardiol Rep. 2014;16(8):511.

25. Ramirez FD, Birnie DH, Nair GM, Szczotka A, Redpath CJ, Sadek MM, et al. Efficacy and safety of driver-guided catheter ablation for atrial fibrillation: a systematic review and meta-analysis. J Cardiovasc Electrophysiol. 2017;28(12):1371-8.

26. Phung TN, Moyer CB, Norton PT, Ferguson JD, Holmes JW. Effect of ablation pattern on mechanical function in the atrium. Pacing Clin Electrophysiol. 2017;40(6):648-54.

27. Pilote, L, Hüttner I, Marpole D, Sniderman A. Stiff left atrial syndrome. Can J Cardiol. 1988;4(6):255-7.

28. Gibson DN, Di Biase L, Mohanti P, Patel JD, Bai R, Sanchez J, et al: Stiff left atrial syndrome after catheter ablation for atrial fibrillation: clinical characterization, prevalence, and predictors. Heart Rhythm. 2011;8(9):1364-71.

29. Wylie JV, Peters DC, Essebag V, Manning WJ, Josephson ME, Hauser TH. Left atrial function and scar after catheter ablation of atrial fibrillation. Heart Rhythm. 2008;5(5):656-62.

30. Sandhu A, Zipse MM, Borne RT, Aleong RG, Tompkins C, Schuller J, et al. Esophageal position, measured luminal temperatures, and risk of atrioesophageal fistula with atrial fibrillation ablation. Pacing Clin Electrophysiol. 2019;42(4):458-63.

31. Aupperle H, Doll N, Walther T, Kornherr P, Ullmann C, Schoon HA, et al. Ablation of atrial fibrillation and esophageal injury: effects of energy source and ablation technique. J Thorac Cardiovasc Surg. 2005;130(6):1549-54.

32. Medeiros De Vasconcelos JT, Filho SDSG, Atié J, Maciel W, De Souza OF, Saad EB, et al. Atrial-oesophageal fistula following percutaneous radiofrequency catheter ablation of atrial fibrillation: the risk still persists. Europace. 2017;19(2):250-8.

33. Scanavacca M. Current atrial fibrillation ablation: an alert for the prevention and treatment of esophageal lesions. Arq Bras Cardiol. 2016;106(5):354-7.

34. Chubb H, Karim R, Roujol S, Nuñez-Garcia M, Williams SE, Whitaker J, et al. The reproducibility of late gadolinium enhancement cardiovascular magnetic resonance imaging of post-ablation atrial scar: a cross-over study. J Cardiovasc Magn Reson. 2018;20(1):21.

35. Donal E, Lip GY, Galderisi M, Goette A, Shah D, Marwan M, et al. EACVI/EHRA Expert Consensus Document on the role of multi-modality imaging for the evaluation of patients with atrial fibrillation. Eur Heart J Cardiovasc Imaging. 2016;17(4):355-83.

36. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med. 2015;372(19):1812-22.

37. Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. JAMA. 2014;311(5):498-506.

38. National Heart, Lung, and Blood Institute. ClinicalTrials.gov [Internet]. Efficacy of Delayed Enhancement MRI-Guided Ablation vs Conventional Catheter Ablation of Atrial Fibrillation (DECAAFII). Maryland, USA: NIH; 2019 [cited 17 fev 2018].Available from: https://clinicaltrials.gov/ct2/show/NCT02529319.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Is Magnetic Resonance Imaging Already an Appropriate Method for Evaluating Patients after Atrial Fibrillation Catheter Ablation?

Cristiano F. Pisani and Mauricio Scanavacca

Unidade Clínica de Arritmia do Instituto do Coração (InCor) do Hospital das Clínicas da FM USP (HC-FMUSP), São Paulo, SP - Brazil

Short Editorial related to the article: Extent of Left Atrial Ablation Lesions and Atrial Fibrillation Recurrence after Catheter Ablation – A Systematic Review and Meta-Analysis

For a long time, lack of knowledge regarding the physiopathology of atrial fibrillation (AF) limited the development of interventional techniques for treating it. Demonstrations that paroxysmal AF was triggered by extrasystoles and tachycardias mainly originating from inside the pulmonary veins ushered in a new era for treatment of AF. Since then, electrical isolation of the pulmonary veins has been the standard treatment for AF.[1] Among specialists, achieving lasting electrical isolation of the pulmonary veins has been the main technical challenge, which has gradually been overcome in recent years with the implementation of new technology for more effective ablation, given that reconnections or previously isolated veins are the main cause of recurrences observed in these patients.[2]

The challenge has been greater in patients with persistent AF, owing to its more complex physiopathology, which involves additional mechanisms that are little known, in addition to the pulmonary venous foci. It is known that metabolic alterations induced by excessive atrial work during repeated episodes of AF initially induce atrial electrical remodeling, characterized by functional and transient changes in ion channels of cell membranes that modulate atrial electrical activity, thus facilitating the appearance of trigger foci in other regions of the atria and conditions that favor increased persistence of AF.[3]

Repetition and prolonged duration of AF evolves to atrial anatomical remodeling, characterized by ultra-structural cellular changes that culminate in cellular death and substitution with fibrosis, creating definitive conditions for the development of more complex mechanisms that sustain AF.[4,5] In parallel, there are changes in the activity of the atrial autonomic nervous system (autonomic remodeling), which are another factor for the occurrence of AF. Taken together, these effects predispose to the maintenance of AF, and they generate a condition where it is more difficult to recover stable permanent sinus rhythm.[6]

Based on this information, diverse strategies have been investigated in addition to the isolation of pulmonary veins, such as isolation of the superior vena cava, the posterior wall of the left atrium, the coronary sinus, and the left atrial appendage, as well as the creation of block lines in order to prevent macro-reentrant tachycardias; attempts have also been made to homogenize areas of diseased atrial tissue and to modulate the atrial autonomic nervous system.[7] All of these strategies end up creating scars that will create potential substrates for the appearance of new tachycardias if they are not homogenous.[8]

As with the evaluation of pulmonary vein isolation, the main limitation when evaluating the effectiveness of these procedures has been the absence of effective non-invasive methods for evaluating the quality of scars induced during the ablation procedure. Thus far, invasive electrophysiological examination has been the only method capable of demonstrating that the tissue submitted to ablation has been transformed into electrically inactive tissue (scar), which is effective in isolating or blocking electrical conduction in the area of interest.

Magnetic resonance imaging (MRI) of the left atrium with gadolinium contrast and analysis of areas of fibrosis by late enhancement has been considered the most promising non-invasive method for assessing the atrial scar burden in patients before ablation, by identifying patients with normal atria and higher likelihood of having effective procedures, in relation to those who already have a higher fibrotic burden and a high likelihood of post-procedural recurrence of atrial tachycardias.[9] Another interesting point is that patients who present greater extent of atrial fibrosis are at a higher risk of embolic events. [10]

When MRI is used after ablation, it is capable of evaluating whether thermal lesions caused by ablation resulted in definitive scarring, and it can also identify gaps in scar formation, which are primarily responsible for recurrences after ablation. [11]

In this edition of *Arquivos Brasileiros de Cardiologia*, Correia et al.[12] present a systematic review and meta-analysis of studies that have evaluated the extent of atrial fibrosis with MRI after catheter ablation in patients with AF. The systematic review includes eight observational studies (six with radiofrequency and two with patients also submitted to balloon cryoablation). Six of these studies showed an association between extent of left atrial scarring and lower recurrence of AF after ablation, and the meta-analysis, which included four studies with 319 patients, also confirmed that greater extent of atrial fibrosis after ablation is associated with lower rate of recurrence of atrial arrhythmias (standard mean difference = 0.52; 95% CI: 0.27 – 0.76; $p < 0.0001$).

These data are compatible with the expectation that patients with higher rates of isolation in areas of interest will present

Keywords

Atrial Fibrillation; Catheter Ablation; Atria Premature Complexes; Magnetic Resonance Spectroscopy/methods; Gadolinium.

Mailing Address: Cristiano F Pisani •
Unidade Clínica de Arritmia do Instituto do Coração (InCor) do Hospital das Clínicas da FM USP (HC-FMUSP) - Av. Dr. Eneas Carvalho de Aguiar, 44. Postal Code 05403-000, São Paulo, SP - Brazil
E-mail: cristianopisani@gmail.com

DOI: https://doi.org/10.36660/abc.20200204

greater extent of fibrosis after ablation. However, the study does not make it clear whether this beneficial effect was due to a lower occurrence of gaps in the induced scars or whether it was due to greater extent of ablation, for example, in other areas such as the posterior wall of the left atrium or the atrial septum. Current evidence has shown that extensive scars controlled by new technology that produces more effective and more lasting scars, with fewer reconnections, either by radiofrequency[13] or by cryoablation,[14] are currently improving the results of AF ablation.

For this reason, these results should be interpreted cautiously, given that the creation of extensive atrial scarring that is not homogeneous may even lead to greater recurrence of atrial arrhythmias, especially in cases of scar-related atrial tachycardias, which, in some situations, may even be more symptomatic and complex to manage than AF itself.[8]

An additional complicating factor is the lack of studies demonstrating the reproducibility of analyses of areas of atrial fibrosis when different methods of image evaluation are used, whether or not they use special software for automatic image processing. Accordingly, there are few studies comparing the observations obtained by MRI with electroanatomical maps that effectively guide AF ablations in the initial procedure and in recurrences, including some cases where there was not good agreement between the maps and the scar on MRI.[11]

In conclusion, notwithstanding the great potential shown by images obtained by late gadolinium enhancement MRI, additional studies are necessary to prove its reproducibility and effectiveness for identifying and recognizing characteristics of atrial fibrosis, both during the selection of patients who will undergo AF ablation and in patients who have already undergone the procedure.

References

1. Haissaguerre M, Jais P, Shah DC, Takahashi A, Hocini M, Quiniou G, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. N Engl J Med. 1998;339(10):659-66.
2. Ouyang F, Bansch D, Ernst S, Schaumann A, Hachiya H, Chen M, et al. Complete isolation of left atrium surrounding the pulmonary veins: new insights from the double-Lasso technique in paroxysmal atrial fibrillation. Circulation. 2004;110(15):2090-6.
3. Nattel S. Paroxysmal atrial fibrillation and pulmonary veins: relationships between clinical forms and automatic versus re-entrant mechanisms. Can J Cardiol. 2013;29(10):1147-9.
4. Burstein B, Nattel S. Atrial fibrosis: mechanisms and clinical relevance in atrial fibrillation. J Am Coll Cardiol. 2008;51(8):802-9.
5. Nattel S, Dobrev D. The multidimensional role of calcium in atrial fibrillation pathophysiology: mechanistic insights and therapeutic opportunities. Eur Heart J. 2012;33(15):1870-7.
6. Guichard JB, Nattel S. Atrial Cardiomyopathy: A Useful Notion in Cardiac Disease Management or a Passing Fad? J Am Coll Cardiol. 2017;70(6):756-65.
7. Calkins H, Hindricks G, Cappato R, Kim YH, Saad EB, Aguinaga L, et al. 2017 HRS/EHRA/ECAS/APHRS/SOLAECE expert consensus statement on catheter and surgical ablation of atrial fibrillation. Europace. 2018;20(1):e1-e160.
8. Verma A, Jiang CY, Betts TR, Chen J, Deisenhofer I, Mantovan R, et al. Approaches to catheter ablation for persistent atrial fibrillation. N Engl J Med. 2015;372(19):1812-22.
9. Marrouche NF, Wilber D, Hindricks G, Jais P, Akoum N, Marchlinski F, et al. Association of atrial tissue fibrosis identified by delayed enhancement MRI and atrial fibrillation catheter ablation: the DECAAF study. Jama. 2014;311(5):498-506.
10. King JB, Azadani PN, Suksaranjit P, Bress AP, Witt DM, Han FT, et al. Left Atrial Fibrosis and Risk of Cerebrovascular and Cardiovascular Events in Patients With Atrial Fibrillation. J Am Coll Cardiol. 2017;70(11):1311-21.
11. Bisbal F, Guiu E, Cabanas-Grandio P, Berruezo A, Prat-Gonzalez S, Vidal B, et al. CMR-guided approach to localize and ablate gaps in repeat AF ablation procedure. JACC Cardiovasc Imaging. 2014;7(7):653-63.
12. Correia ETO, Barbetta L, Mesquita ET. Extent of Left Atrial Ablation Lesions and Atrial Fibrillation Recurrence after Catheter Ablation - A Systematic Review and Meta-Analysis. Arq Bras Cardiol. 2020; 114(4):627-635.
13. Phlips T, Taghji P, El Haddad M, Wolf M, Knecht S, Vandekerckhove Y, et al. Improving procedural and one-year outcome after contact force-guided pulmonary vein isolation: the role of interlesion distance, ablation index, and contact force variability in the 'CLOSE'-protocol. Europace. 2018;20(FI_3):f419-f27.
14. Kuck KH, Furnkranz A, Chun KR, Metzner A, Ouyang F, Schluter M, et al. Cryoballoon or radiofrequency ablation for symptomatic paroxysmal atrial fibrillation: reintervention, rehospitalization, and quality-of-life outcomes in the FIRE AND ICE trial. Eur Heart J. 2016;37(38):2858-65.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Impaired Right Ventricular Function in Heart Transplant Rejection

Luciana J. B. M. Carrion,[1] Alice Sperotto,[2] Raffaela Nazario,[1,2] Livia A. Goldraich,[2] Nadine Clausell,[1,2] Luís Eduardo Rohde,[1,2] Angela Barreto Santiago Santos[1,2]

Universidade Federal do Rio Grande do Sul - PPG em Cardiologia,[1] Porto Alegre, RS – Brazil

Hospital de Clínicas de Porto Alegre – Cardiologia,[2] Porto Alegre, RS – Brazil

Abstract

Background: The practice of screening for complications has provided high survival rates among heart transplantation (HTx) recipients.

Objectives: Our aim was to assess whether changes in left ventricular (LV) and right ventricular (RV) global longitudinal strain (GLS) are associated with cellular rejection.

Methods: Patients who underwent HTx in a single center (2015 – 2016; n = 19) were included in this retrospective analysis. A total of 170 biopsies and corresponding echocardiograms were evaluated. Comparisons were made among biopsy/echocardiogram pairs with no or mild (0R/1R) evidence of cellular rejection (n = 130 and n = 25, respectively) and those with moderate (2R) rejection episodes (n=15). P-values < 0.05 were considered statistically significant

Results: Most patients were women (58%) with 48 ± 12.4 years of age. Compared with echocardiograms from patients with 0R/1R rejection, those of patients with 2R biopsies showed greater LV posterior wall thickness, E/e' ratio, and E/A ratio compared to the other group. LV systolic function did not differ between groups. On the other hand, RV systolic function was more reduced in the 2R group than in the other group, when evaluated by TAPSE, S wave, and RV fractional area change (all p < 0.05). Furthermore, RV GLS (−23.0 ± 4.4% in the 0R/1R group vs. −20.6 ± 4.9% in the 2R group, p = 0.038) was more reduced in the 2R group than in the 0R/1R group.

Conclusion: In HTx recipients, moderate acute cellular rejection is associated with RV systolic dysfunction as evaluated by RV strain, as well as by conventional echocardiographic parameters. Several echocardiographic parameters may be used to screen for cellular rejection. (Arq Bras Cardiol. 2020; 114(4):638-644)

Keywords: Ventricular Dysfunction, Right; Heart Transplantation; Graft Rejection; Echocardiography/methods; Strain; Speckle Tracking.

Introduction

Over the last five decades, heart transplantation (HTx) has become an established therapeutic option for patients with end-stage heart failure.[1,2] Improvements in surgical techniques, patient selection, immunosuppressive drugs, and post-HTx protocols have contributed to the success of this therapy and increased patient survival.[2-5]

Post-HTx follow-up is focused on active screening for complications. Periodic endomyocardial biopsies can diagnose most cases of acute cellular rejection (ACR), in which patients are mostly asymptomatic, and left ventricular ejection fraction (LVEF) remains normal.[2,6] However, endomyocardial biopsy is an invasive and costly procedure with potentially serious complications.[2,7-9] The search for other methods that can screen for rejection is thus becoming increasingly important.

A few studies on novel echocardiographic techniques, such as two-dimensional speckle-tracking echocardiography (2D STE), have shown that reduction of left ventricular (LV) global longitudinal strain (GLS) is associated with graft rejection, and it can be used to detect early subclinical myocardial dysfunction. However, there is no consensus in the literature in relation to the clinical applicability of GLS assessment in this scenario.[2-6,10] Furthermore, little is known about right ventricular (RV) GLS and its potential role in rejection, highlighting the research gaps in this area.[10-12]

Seeking to expand current knowledge about early myocardial dysfunction and graft rejection, the present study was designed to evaluate whether changes in myocardial strain by speckle tracking are associated with ACR. Specifically, we aimed to evaluate whether reduced LV GLS and RV GLS are associated with cardiac graft rejection.

Methods

Study Population

All adult patients (age > 18 years) who underwent HTx at the Hospital de Clínicas in Porto Alegre, Rio Grande do Sul, Brazil, between 2015 and 2016 were included in this analysis. During this period, patients received routine

Mailing Address: Angela Barreto Santiago Santos •
Hospital de Clinicas de Porto Alegre – Cardiologia - Rua Ramiro Barcelos, 2350, Sala 2061. Postal Code 90035-903, Porto Alegre, RS – Brazil
E-mail: abssantos@hcpa.edu.br
Manuscript received January 24, 2019, revised manuscript May 03, 2019, accepted June 05, 2019

DOI: https://doi.org/10.36660/abc.20190054

monitoring per hospital protocol, and their data were analyzed during the first 18 months of follow-up after HTx. Of the 20 patients who received transplants (all via the bicaval technique), 19 were included in this analysis, and one patient who died before the first endomyocardial biopsy due to hyperacute graft rejection was excluded. The standard institutional follow-up protocol, which served as a guide for this study, consisted of weekly biopsies in the first month post-HTx; biopsies every other week during the second and third months post-HTx; monthly biopsies from the fourth to the sixth month post-HTx; and subsequent biopsies every three to four months until 18 months of follow-up had been completed. Each biopsy was followed by echocardiography, seeking to detect post-biopsy complications.

Of the 257 biopsies performed up to July 2017, 170 had corresponding echocardiograms with images suitable for strain analysis by the speckle-tracking method and were thus included in this study (Figure 1). Comparisons were made among biopsy/echocardiogram pairs with no (0R) or mild (1R) evidence of rejection (n = 130 and n = 25, respectively) and those with moderate (2R) rejection episodes (n = 15). This study was conducted in accordance with the standards set out in the Declaration of Helsinki, and its protocol was approved by the institutional Research Ethics Committee.

Echocardiographic Analysis

All echocardiograms were recorded and analyzed offline on a TOMTEC workstation (TomTec Imaging Systems, Unterschleißheim, Germany) by an experienced echocardiographer (LJBMC) blinded to clinical data and to the corresponding biopsies. Measurements were obtained according to American Society of Echocardiography (ASE) standards, including septal and posterior wall thicknesses; diameters of the LV, RV, aorta, and left atrium; transmitral flow; mitral and tricuspid annular relaxation velocities; and tricuspid annular excursion.

Echocardiographic measures of RV function were performed using the apical 4-chamber view. Tricuspid annular plane systolic excursion (TAPSE) was measured as the vertical displacement of the tricuspid annulus from end-diastole to end-systole using M-mode. The tissue Doppler-derived tricuspid lateral annular systolic velocity wave (S wave) was obtained aligning the basal segment and the tricuspid annulus with the Doppler cursor. RV fractional area change (FAC) was evaluated by manual tracing of RV areas as follows: (RV end-diastolic area − RV end-systolic area) / RV end-diastolic area × 100.

Analysis of myocardial deformation (GLS) was performed using specific B-mode speckle-tracking software for the LV and the RV (2D CPA TTA2.20.01, TomTec). This software circumvents angle dependency and identifies cardiac motion by tracking multiple reference points over time. At end-systole, as defined by ECG, three landmarks were established at the endocardial edge (two basal and one apical), with automatic detection of speckles along the endocardial edge of the specified cavity (LV or RV). Manual adjustments were made when necessary. In the LV, peak-systolic strain for each 2D apical view (two-, three-, and four-chamber) was automatically obtained from the mean of the 6 traced segments, while LV GLS was obtained by averaging the peak-systolic strain of apical views. In the RV, RV GLS was defined as the peak-systolic strain that combined the free wall and the septum (Figure 2). All patients were in sinus rhythm, and a single cardiac cycle was analyzed. Images in which poor quality precluded speckle analysis in two or more consecutive segments, images covering less than one complete cardiac cycle, or excessively tangential views were excluded. LV and RV end-systolic and end-diastolic volumes were used to derive other measures of myocardial function, such as LVEF (by the modified Simpson method) and RV FAC.

Intraobserver variability for LV GLS and RV GLS was assessed in a sample of 20 randomly selected echocardiograms. The coefficient of variation was 3.8% and 6.7% for LV GLS and RV GLS, respectively. Intraclass correlation coefficients were 0.96 for LV GLS (95% confidence interval: 0.91 – 1.0) and 0.80 for RV GLS (95% confidence interval: 0.59 – 1.0).

Endomyocardial Biopsy

Endomyocardial biopsies were scheduled as required by the standard institutional protocol. All were performed through an internal jugular vein access, at the catheterization laboratory. During the procedure, a sheath was advanced to the interventricular septum through the tricuspid valve, and 3 – 6 small fragments were retrieved with a cardiac bioptome for histological analysis. Tissue samples were evaluated by a single experienced pathologist who was blinded to the results of the echocardiographic studies. Biopsies were examined for ACR, graded on a scale from 0R to 3R, according to the International Society for Heart and Lung Transplantation (ISHLT) classification.[13] All patients with biopsies classified as ≥ 2R were treated with a standard regimen for rejection, while those with biopsies classified as 1R were monitored closely and remained on maintenance immunosuppression therapy, following institutional protocols.

Statistical Analysis

Normally distributed continuous data were expressed as means and standard deviations, and categorical data were shown as absolute and relative frequencies. Echocardiography variables were compared using ANOVA adjusted for each HTx patient accounting for repeated measurements. All statistical analyses were performed in the SPSS software package. All tests were two-sided, and p-values < 0.05 were considered statistically significant.

Results

Most HTx recipients (n = 19) followed in this study were women (n = 11; 58%), with a mean age of 48 ± 12.4 years. In general, few had other comorbidities, and the main etiology of heart failure was of non-ischemic origin. Donors were mostly young men, with a mean age of 29 years (Table 1).

Of the 257 biopsies performed in this period, the results of 66% (n = 170) correlated with echocardiography. Of the biopsies excluded from analysis (87 without corresponding echocardiograms), 24 showed 1R rejection; two showed 2R rejection; and one showed 3R rejection. Of the 170 biopsies

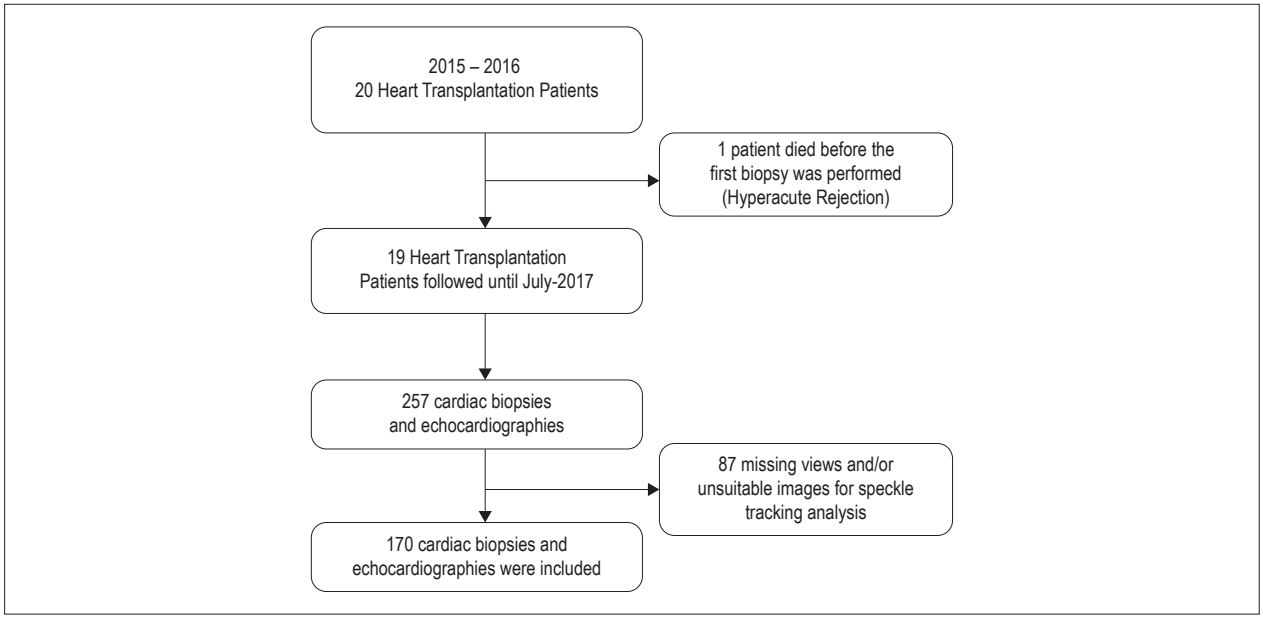


Figure 1 – *Feasibility of strain evaluation by speckle-tracking analysis.*

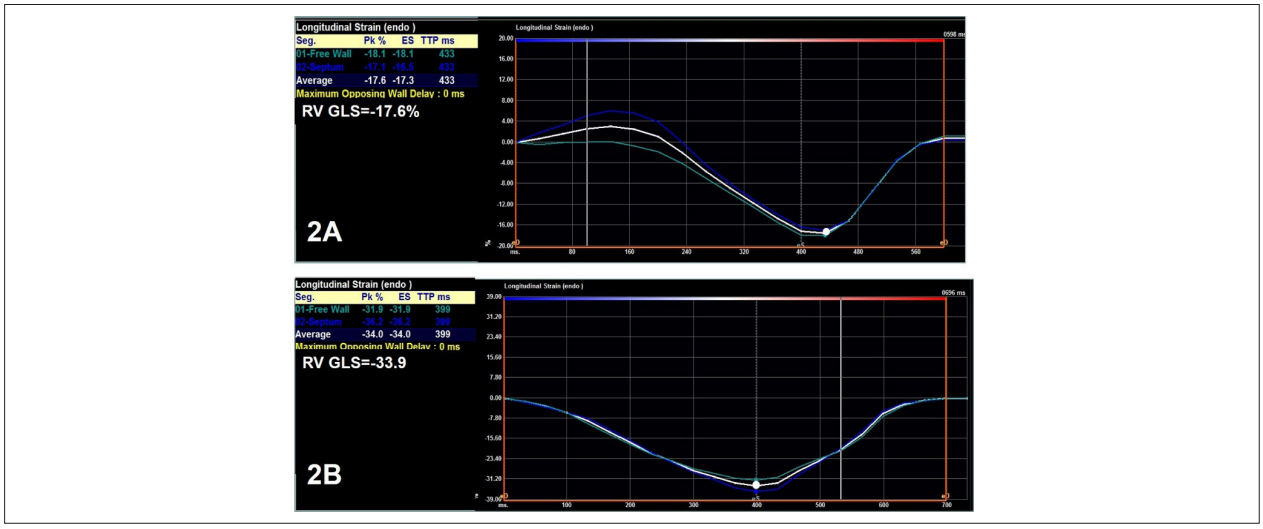


Figure 2 – *Two-dimensional speckle tracking imaging for right ventricular analysis in a heart transplant recipient at the time of biopsy-proven 2R rejection (Panel 2A) and the same patient at the time of biopsy without rejection (Panel 2B). Curves represent longitudinal strain curves and the white dot represents peak-systolic strain, which were used to measure right ventricular systolic function.*

analyzed in this study, 15 biopsies from 12 HTx recipients showed 2R rejection, and 155 biopsies showed either no evidence of cellular rejection or 1R rejection (n = 130 and n = 25, respectively).

Heart Structure and Function

Compared to exams from patients without rejection or 1R rejection, echocardiograms from corresponding biopsies with 2R rejection episodes revealed greater LV posterior wall thickness, which did not reflect in an increase in LV mass or relative wall thickness. In exams from patients with 2R rejection, measures of diastolic function showed an increase in the medial and lateral E/e' ratio and the E/A ratio (Table 2).

LV systolic function did not differ between groups when evaluated by the traditional method (LVEF) or by LV GLS (−20.2 ± 3.3% in the 0R/1R group vs. −19.5 ± 3.3% in the 2R group, p = 0.351). On the other hand, RV systolic function was reduced in the 2R group, in comparison with the other group, when evaluated by TAPSE, S wave and RV FAC. Additionally, RV GLS (−22.97 ± 4.4% in the 0R/1R group vs. −20.6 ± 4.9% in the 2R group, p = 0.038) was reduced in the 2R group, in comparison with the 0R/1R group (Figure 3).

Table 1 – Baseline characteristics of the study population

Variable	Value
HTx recipientes (n = 19)	
Male sex, n (%)	8 (42%)
Age at transplantation (years)	47.7 ± 12.4
Comorbidities	
Diabetes, n (%)	5 (25%)
Hypertension, n (%)	4 (20%)
Obesity, n (%)	4 (20%)
Stroke, n (%)	5 (25%)
Dyslipidemia, n (%)	1 (5%)
Peripheral vascular disease, n (%)	3 (15%)
Current smoker, n (%)	7 (35%)
Time to HTx (days)	80 ± 105
Ischemic time before HTx (min)	225 ± 57
Heart failure etiology	
Ischemic heart disease, n (%)	2 (10%)
Non-ischemic cardiomyopathy, n (%)	17 (89%)
Donor	
Men, n (%)	13 (65%)
Age (years)	29 ± 7.6
Body surface area (m^2)	1.78 ± 1.4
Current smoker, n (%)	0 (0%)

Data shown as mean ± SD or n (%). Number of patients = 19. HTx: heart transplantation.

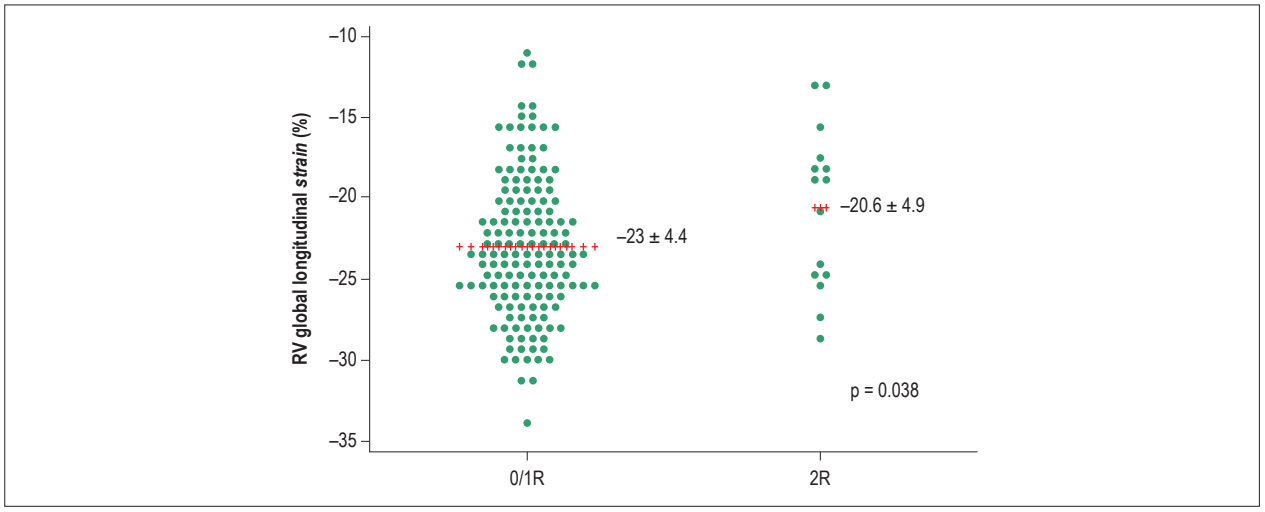


Figure 3 – *Distribution of rejection on cardiac biopsies over RV GLS strain results after heart transplantation.*

Discussion

In this retrospective analysis of 170 matched echocardiograms and endomyocardial biopsies of post-HTx patients, our main finding was that moderate (2R) cellular rejection was associated with RV contractile dysfunction when assessed by RV GLS, as well as by conventional echocardiographic parameters such as TAPSE, S wave, and FAC. Conversely, LV systolic function was unchanged in this group. In addition, moderate rejection was associated with increased LV posterior wall thickness, E/e' ratio, and E/A ratio.

In the search for noninvasive methods to aid in screening for cellular rejection, a few studies evaluated strain and strain rate

Table 2 – Cardiovascular structure and function

Variables	0R/1R N = 155	2R N = 15	p-value
Aortic diameter (mm)	33.0 ± 4.1	32.4 ± 5.7	0.575
Left atrial diameter (mm)	40.8 ± 5.6	42.5 ± 7.7	0.372
IS thickness (mm)	11.2 ± 1.4	11.5 ± 1.6	0.439
PW thickness (mm)	10.4 ± 1.4	11.3 ± 1.5	0.013
Relative wall thickness	0.49 ± 0.08	0.53 ± 0.08	0.115
LV end-diastolic diameter (mm)	42.4 ± 4.1	43.0 ± 2.7	0.550
LV end-systolic diameter (mm)	28.2 ± 4.4	28.3 ± 3.7	0.936
LV end-diastolic volume (mL)	88.2 ± 24.3	84.6 ± 18.0	0.593
LV end-systolic volume (mL)	35.7 ± 12.9	37.2 ± 12.9	0.618
RV basal diameter (mm)	40.2 ± 4.4	40.9 ± 2.9	0.550
RV end-diastolic area (cm^2)	20.2 ± 4.3	21.4 ± 3.8	0.302
RV end-systolic area (cm^2)	10.9 ± 3.1	12.8 ± 3.8	0.024
LV mass (g)	157.2 ± 33.9	173.9 ± 33.7	0.057
LV ejection fraction, Teichholz (%)	62.3 ± 7.9	63.2 ± 8.4	0.714
LV ejection fraction, Simpson (%)	59.6 ± 7.9	56.5 ± 8.6	0.122
TAPSE (mm)	13.8 ± 3.4	10.9 ± 2.2	0.009
RV fractional area change (cm/s)	46.2 ± 8.6	40.8 ± 10.2	0.016
E/A	1.56 ± 0.55	2.07 ± 0.82	0.017
Deceleration time (ms)	183.0 ± 41.8	158.2 ± 20.8	0.157
Medial e' (cm/s)	7 ± 2	7 ± 2	0.653
Lateral e' (cm/s)	12 ± 3	9 ± 2	0.100
Medial E/e'	11.9 ± 4.4	20.6 ± 4.4	0.001
Lateral E/e'	7.6 ± 3.5	13.3 ± 5.2	0.006
S wave (cm/s)	10.0 ± 2.1	8.3 ± 1.8	0.035
LV global longitudinal strain (%)	−20.2 ± 3.3	−19.5 ± 3.3	0.351

Data are shown as mean ± SD. P-value calculated by ANOVA adjusted for heart transplantation patients. E/A: early to late mitral inflow velocity ratio; e': mitral relaxation velocity; E/e': mitral inflow to mitral relaxation velocity ratio; IS: interventricular septal; LV: left ventricular; PW: posterior wall; RV: right ventricular; S wave: tricuspid lateral systolic velocity; TAPSE: tricuspid annular plane systolic excursion.

by tissue Doppler imaging (TDI). Marciniak et al.,[10] studying a group of 31 patients with 106 biopsy/echocardiogram pairs, demonstrated a decrease in strain and strain rate on TDI in basal and apical segments of the RV free wall and in basal and middle segments of the LV lateral wall in the group with ≥ 1B rejection, suggesting that these findings could be an additional tool for detecting acute rejection. The same authors also observed that, when histopathological involvement was mild (< 2B), these alterations took on a pattern of segmental involvement, with little or no impact on GLS, revealing a low sensitivity of the latter for low-grade rejection.[10] More recently, the advent of evaluation of regional or global myocardial function by speckle tracking has provided a more robust technique for the detection of subclinical myocardial dysfunction, overcoming the limitations of TDI-measured strain, especially the dependence on prospective acquisition and the angle of acquisition.[10,11] At least three studies, published almost concomitantly, showed a rejection-related decrease in LV GLS,[14-16] while another group, as in our study, found no such differences in LV GLS when comparing exams from patients with no rejection or mild rejection to patients with moderate rejection.[17] It bears stressing that, even in the 0R group of our study, LV GLS values exceeded the range reported as normal after HTx in the literature.[18,19]

Evaluation of RV parameters as potential markers of subclinical rejection was relatively less explored in previous studies. Clemmensen et al. studied a group of 36 HTx recipients and found that TAPSE was reduced in the group with cellular rejection.[16] Another group, which studied a similar number of patients (n = 34), found a reduction in RV free wall strain associated with ≥ 2R rejection.[15] These findings were observed as a similar trend in our study, where the decrease in RV function was shown by TAPSE, S wave, FAC, and RV peak GLS in moderate rejection. Eleid et al. demonstrated a decline in LV GLS in the early post-HTx period, and the association of non-improvement in GLS throughout follow-up was an independent predictor of worse prognosis for these patients, regardless of the histopathological results of endomyocardial biopsies.[20]

In addition, the early post-Htx period is a time of adaptation of the new heart to the thoracic space, in a different position in the chest compared to the native heart, with expected structural alterations like increase of LV mass and in wall thickness due to inflammatory cell infiltration and graft edema, which are part of the physiological process of Htx. These abnormalities improve gradually within the first 6 months after transplant, but they can be a confounders of some signs of graft rejection.

Furthermore, in agreement with the findings of our study, LV hypertrophy and changes in diastolic function, especially in LV filling pressure, have been associated with cellular rejection, despite the lower sensitivity of these findings, which may be confused with usual post-HTx alterations.[15,18]

Some limitations of this analysis should be noted. As most echocardiographies for which corresponding biopsies were available had been performed to detect complications of endomyocardial biopsy, such as pericardial effusion and tricuspid valve injury, many failed to include a detailed evaluation of cardiac function and dynamics. As a consequence, we had to exclude 34% of biopsies. The single-center design of this study is also a limitation, especially because it was performed at a facility that is still expanding its HTx program, which accounts for the small sample size. Information on antibody-mediated rejection was not included in this study; therefore, echocardiographic findings cannot be extrapolated for that situation. Overall, the study comprised a low immunological risk population.

Conclusions

In conclusion, we found evidence of RV systolic dysfunction in post-HTx patients with moderate rejection by 2D STE assessment of strain, as well as by conventional echocardiographic methods, in comparison with patients with no significant signs of rejection on histopathology. LV systolic function remained unchanged, suggesting that subclinical LV dysfunction may arise later than RV dysfunction. Moreover, patients with biopsy evidence of moderate rejection had greater LV hypertrophy and worse LV diastolic function and filling pressure on echocardiography. The role of these findings in screening for and diagnosing rejection, perhaps even leading to practice-changing updates in endomyocardial biopsy protocols, has yet to be explored in a prospective multicenter study.

Author contributions

Conception and design of the research and Analysis and interpretation of the data: Carrion LFBM, Rohde LE, Santos ABS; Acquisition of data, Statistical analysis and Writing of the manuscript: Carrion LFBM, Santos ABS; Critical revision of the manuscript for intellectual content: Sperotto A, Nazario R, Goldraich LA, Clausell N.

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 Luciana J. B. M. Carrion, from Universidade Federal do Rio Grande do Sul.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the UFRGS – Hospital de Clínicas de Porto Alegre under the protocol number CAAE 68562717.9.0000.5327. 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.

References

1. 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. 2017;36(10):1037-46.
2. Badano LP, Miglioranza MH, Edvardsen T, Colafranceschi AS, Muraru D, Bacal F, et al. European Association of Cardiovascular Imaging/ Cardiovascular Imaging Department of the Brazilian Society of Cardiology recommendations for the use of cardiac imaging to assess and follow patients after heart transplantation. Eur Heart J Cardiovasc Imaging. 2015;16(9):919-48.
3. Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, Desai S, et al. The International Society of Heart and Lung Transplant Guidelines for the care of heart transplant recipients. J Heart Lung Transplant. 2010;29(8):914-56.
4. Clemmensen TS, Munk K, Tram EM, Ilkjaer LB, Severinsen IK, Eiskjaer H. Twenty years' experience at the Heart Transplant Center, Aarhus University Hospital, Skejby, Denmark. Scand Cardiovasc J. 2013;47(6):322-8.
5. Stehlik J, Edwards LB, Kucheryavaya AY, Benden C, Christie JD, Dipchand AI, et al. The Registry of the International Society for Heart and Lung Transplant: 29th Official Adult Heart Transplant Report-2012. J Heart Lung Transplant. 2012;31(10):1052-64.
6. Streeter RP, Nichols K, Bergmann SR. Stability of right and left ventricular ejection fractions and volumes after heart transplantation. J Heart Lung Transplant. 2005;24(7):815-8.
7. Baraldi-Jenkins C, Levin HR, Kasper EK, Rayburn BK, Herskowitz A, Baughman KL. Complications of endomyocardial biopsy in heart transplant patients. J Heart Lung Transplant. 1993;12(1 Pt 1):63-7.
8. Cooper LT, Baughman KL, Feldman AM, Frustaci A, Jessup M, Kuhl U, et al. The role of endomyocardial biopsy in the management of cardiovascular disease: a scientific statement from the American Heart Association, the American College of Cardiology, and the European Society of Cardiology. Circulation. 2007;116(19):2216-33.

9. Yilmaz A, Kindermann I, Kindermann M, Mahfoud F, Ukena C, Athanasiadis A, et al. Comparative evaluation of left and right ventricular endomyocardial biopsy: differences in complication rate and diagnostic performance. Circulation. 2010;122(9):900-9.

10. Marciniak A, Eroglu E, Marciniak M, Sirbu C, Herbots L, Droogne W, et al. The potential clinical role of ultrasonic strain and strain rate imaging in diagnosing acute rejection after heart transplantation. Eur J Echocardiogr. 2007;8(3):213-21.

11. Kato TS, Oda N, Hashimura K, Hashimoto S, Nakatani T, Ueda HI, et al. Strain rate imaging would predict sub-clinical acute rejection in heart transplant recipients. Eur J Cardiothorac Surg. 2010;37(5):1104-10.

12. Sato T, Kato TS, Kamamura K, Hashimoto S, Shishido T, Mano A, et al. Utility of left ventricular systolic torsion derived from 2-dimensional speckle-tracking echocardiography in monitoring acute cellular rejection in heart transplant recipients. J Heart Lung Transplant. 2011;30(5):536-43.

13. Stewart S, Winters GL, Fishbein MC, Tazelaar HD, Kobashigawa J, Abrams J, et al. Revision of the 1990 working formulation for the standardization of nomenclature in the diagnosis of heart rejection. J Heart Lung Transplant. 2005;24(11):1710-20.

14. Clemmensen T.S., Løgstrup B.B., Eiskjær H., Poulsen S.H. Changes in longitudinal myocardial deformation during acute cardiac rejection: the clinical role of two-dimensional speckle-tracking echocardiography. J Am Soc Echocardiogr. 2015;28(3):330-9.

15. Mingo SS, Moñivas VP, Lunar IG, Mitroi CD, Goirigolzarri JA, Rivero B, et al. Usefulness of two-dimensional strain parameters to diagnose acute rejection after heart transplantation. J Am Soc Echocardiogr. 2015;28(10):1149-56.

16. Clemmensen TS, Løgstrup BB, Eiskjær H, Poulsen SH. Serial changes in longitudinal graft function and implications of acute cellular graft rejections during the first year after heart transplantation. Eur Heart J Cardiovasc Imaging. 2016;17(2):184-93.

17. Ortiz MR, Peña ML, Mesa D, Delgado M, Romo E, Santisteban M, et al. Impact of asymptomatic acute cellular rejection on left ventricle myocardial function evaluated by means of two-dimensional speckle tracking echocardiography in heart transplant recipients. Echocardiography. 2015;32(2):229-37.

18. Ingvarsson A, WertherEvaldsson A, Waktare J, Nilsson J, Smith GJ, Stagmo M, et al. Normal reference ranges for transthoracic echocardiography following heart transplantation. J Am Soc Echocardiogr. 2018;31(3):349-60.

19. Antończyk K, Niklewski T, Antończyk R, Zakliczyński M, Zembala M, Kukulski T. Evaluation of the graft mechanical function using speckle-tracking echocardiography during the first year after orthotropic heart transplantation. Ann Transplant. 2018 Aug 8;23:554-60.

20. Eleid MF, Caracciolo G, Cho EJ, Scott RL, Steidley DE, Wilansky S, et al. Natural history of left ventricular mechanics in transplanted hearts: relationships with clinical variables and genetic expression profiles of allograft rejection. JACC Cardiovasc Imaging. 2010;3(10):989-1000.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Heart Transplantation and the "The Secret Chamber": How Echocardiographic Assessment of the Right Ventricle Can Reveal Acute Cell Rejection

Henrique Turin Moreira[1] *and Minna Moreira Dias Romano*[1]

Faculdade de Medicina de Ribeirão Preto USP, Ribeirão Preto,[1] *SP – Brazil*

Short Editorial related to the article: Impaired Right Ventricular Function in Heart Transplant Rejection

Although heart transplantation (Tx) has achieved great technical and scientific evolution in recent decades, acute cell rejection (ACR) still represents an important threat to patients submitted to this procedure. Acute rejection screening protocols associated with early immunosuppressive therapy are essential for Tx success. However, endomyocardial biopsy, although expensive and invasive, is still a reference method for the screening of ACR.

ACR is related to incipient damage in myocardial function,[1] which may not be detected by conventional echocardiographic techniques for myocardial function analysis. Myocardial deformation, analyzed by the speckle tracking technique, is able to detect incipient myocardial dysfunction in several pathologies, among them, ACR after cardiac Tx.[2]

In a recent meta-analysis of 10 studies with methodological similarities, Elkaryone et al.[3] analyzed 511 patients and 1,267 endomyocardial biopsies. The sensitivity of the global longitudinal deformation of the left ventricle (LV), expressed by the GLS, to detect ACR diagnosed by endomyocardial biopsy was 78%, with a specificity of 68%.[3] Moreover, changes in LV myocardial deformation have already been demonstrated as independent predictors of clinical outcomes after heart Tx.[4] It is important to note that echocardiographic images do not always allow the analysis of myocardial deformation in this population, since the transplanted heart may be in more medial position in the thoracic cavity, making it difficult to obtain good quality images, as previously demonstrated.[2] However, despite studies of LV changes in this scenario, less knowledge has been accumulated to date about the correlations between changes in the right ventricle (RV) and ACR after heart Tx. The increase in the dimensions of this chamber associated with the slight reduction of its systolic function in the natural evolution of patients after cardiac Tx has been established.[5-7]

The work by Carrion et al.[8] demonstrate that patients with signs of significant ACR by endomyocardial biopsy have reduced left ventricular diastolic function parameters, in addition to signs of increased LV posterior wall thickness, when compared to those without significant rejection. Unlike other studies, there was no significant difference in the LV longitudinal deformation between this group and the one that did not show signs of significant rejection. It is worth mentioning that most of the previous studies used, for the analysis of myocardial deformation, vendor-dedicated software, while Carrion et al.[8] used vendor-independent software to analyze the images,[8] which could explain the aforementioned differences, at least in part, since there is still no standardization between software from different vendors.[8]

Another possible source of divergence between the present study and previous investigations is the methodology used to measure myocardial deformation. Carrion et al.[8] performed the measurement at the systolic peak of myocardial deformation, as recommended by the most recent international guidelines,[9] while other studies used the peak myocardial deformation of the entire cardiac cycle.[9] Also, the software used for the analysis by Carrion et al. is based on the analysis of endocardial deformation, while other software available, and historically more often used, analyzed the myocardial deformation of the entire wall thickness, including all its layers, also called transmural deformation.[10] In this study, the conventional echocardiographic parameters for the analysis of the RV function, as well as the RV myocardial deformation, were significantly reduced in the group of patients with signs of ACR, when compared to those without significant rejection.[11] Moreover, the group with moderate ACR also showed changes suggestive of worse LV diastolic function, when compared to the group without significant rejection.

Thus, the question remains whether the involvement of RV systolic function is a primary one, due to ACR, or secondary to the retrograde increase in LV filling pressures. Additionally, not only the myocardial deformation of the RV, but also the conventional parameters for the functional evaluation of this cardiac chamber have shown be significantly different between the two groups studied by Carrion et al.[8] Previous studies have shown that RV systolic deformation, especially of its free wall, has a greater correlation with RV systolic function, assessed by reference methods, in comparison with conventional echocardiographic parameters, both in ischemic and non-ischemic heart diseases.[12-14] Although the comparison of the diagnostic accuracy of the RV functional parameters for ACR diagnosis has not been addressed by Carrion et al.,[8] this issue is a relevant point to be clarified in future studies, aiming to guide the use of these techniques in the post-heart Tx clinical routine.

Thus, for a science that recently managed to recognize and "point" to the "chamber of secrets", i.e., the RV, the

Keywords

Cellular Acute Rejection; Heart Transplantation; Endomyocardial Biopsy; Graft Rejection; Echocardiography/methods

Mailing Address: Minna Moreira Dias Romano • Campus Universitário HCRP-USP - Postal Code 14048-900
E-mail: minna@fmrp.usp.br

DOI: https://doi.org/10.36660/abc.20200177

work of Carrion et al.[8] reinforces the importance of its echocardiographic evaluation for the non-invasive detection of incipient myocardial dysfunction related to ACR in patients being followed after heart Tx.

References

1. Ruiz Ortiz M, Pena ML, Mesa D, Delgado M, Romo E, Santisteban M, et al. Impact of asymptomatic acute cellular rejection on left ventricle myocardial function evaluated by means of two-dimensional speckle tracking echocardiography in heart transplant recipients. Echocardiography. 2015;32(2):229-37.
2. Badano LP, Miglioranza MH, Edvardsen T, Colafranceschi AS, Muraru D, Bacal F, et al. European Association of Cardiovascular Imaging/Cardiovascular Imaging Department of the Brazilian Society of Cardiology recommendations for the use of cardiac imaging to assess and follow patients after heart transplantation. Eur Heart J Cardiovasc Imaging. 2015;16(9):919-48.
3. Elkaryoni A, Altibi AM, Khan MS, Okasha O, Ellakany K, Hassan A, et al. Global longitudinal strain assessment of the left ventricle by speckle tracking echocardiography detects acute cellular rejection in orthotopic heart transplant recipients: A systematic review and meta-analysis. Echocardiography. 2020;37(2):302-9.
4. Kobayashi Y, Sudini NL, Rhee JW, Aymami M, Moneghetti KJ, Bouajila S, et al. Incremental Value of Deformation Imaging and Hemodynamics Following Heart Transplantation: Insights From Graft Function Profiling. JACC Heart Fail. 2017;5(12):930-9.
5. Ingvarsson A, Werther Evaldsson A, Waktare J, Nilsson J, Smith GJ, Stagmo M, et al. Normal Reference Ranges for Transthoracic Echocardiography Following Heart Transplantation. J Am Soc Echocardiogr. 2018;31(3):349-60.
6. Monivas Palomero V, Mingo Santos S, Goirigolzarri Artaza J, Rodriguez Gonzalez E, Restrepo Cordoba MA, Jimenez Sanchez D, et al. Two-Dimensional Speckle Tracking Echocardiography in Heart Transplant Patients: Two-Year Follow-Up of Right and Left Ventricular Function. Echocardiography. 2016;33(5):703-13.
7. Harrington JK, Richmond ME, Woldu KL, Pasumarti N, Kobsa S, Freud LR. Serial Changes in Right Ventricular Systolic Function Among Rejection-Free Children and Young Adults After Heart Transplantation. J Am Soc Echocardiogr. 2019;32(8):1027-35 e2.
8. Carrion JBM, Sperotto A, Nazario R, Goldraich L, Clausell N, Rohde LE, et al. Disfunção ventricular direita e rejeição do transplante cardíaco. Arq Bras Cardiol. 2020; 114(4):638-644.
9. Farsalinos KE, Daraban AM, Unlu S, Thomas JD, Badano LP, Voigt JU. Head-to-Head Comparison of Global Longitudinal Strain Measurements among Nine Different Vendors: The EACVI/ASE Inter-Vendor Comparison Study. J Am Soc Echocardiogr. 2015;28(10):1171-81, e2.
10. Ruiz-Ortiz M, Rodriguez-Diego S, Delgado M, Kim J, Weinsaft JW, Ortega R, et al. Myocardial deformation and acute cellular rejection after heart transplantation: Impact of inter-vendor variability in diagnostic effectiveness. Echocardiography. 2019;36(12):2185-94.
11. Voigt JU, Pedrizzetti G, Lysyansky P, Marwick TH, Houle H, Baumann R, et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging. J Am Soc Echocardiogr. 2015;28(2):183-93.
12. Becker M, Hoffmann R, Kuhl HP, Grawe H, Katoh M, Kramann R, et al. Analysis of myocardial deformation based on ultrasonic pixel tracking to determine transmurality in chronic myocardial infarction. Eur Heart J. 2006;27(21):2560-6.
13. Moreira HT, Volpe GJ, Marin-Neto JA, Nwabuo CC, Ambale-Venkatesh B, Gali LG, et al. Right Ventricular Systolic Dysfunction in Chagas Disease Defined by Speckle-Tracking Echocardiography: A Comparative Study with Cardiac Magnetic Resonance Imaging. J Am Soc Echocardiogr. 2017;30(5):493-502.
14. Lemarie J, Huttin O, Girerd N, Mandry D, Juilliere Y, Moulin F, et al. Usefulness of Speckle-Tracking Imaging for Right Ventricular Assessment after Acute Myocardial Infarction: A Magnetic Resonance Imaging/Echocardiographic Comparison within the Relation between Aldosterone and Cardiac Remodeling after Myocardial Infarction Study. J Am Soc Echocardiogr. 2015;28(7):818-27 e4.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Original Article

Hydrotherapy Reduces Arterial Stiffness in Pregnant Women With Chronic Hypertension

Giovana Macêdo Linhares,[1] Antonio Vieira Machado,[1] Marcus Vinícius Bolívar Malachias[1]

Faculdade de Ciências Médicas de Minas Gerais, Instituto de Pesquisas e Pós-Graduação,[1] Belo Horizonte, MG – Brazil

Abstract

Background: Chronic hypertension (CH) and high arterial stiffness (AS) increase the risk of complications during pregnancy, such as superimposed preeclampsia and low fetal growth.

Objective: To evaluate the impact of hydrotherapy, a non-pharmacological treatment strategy, on AS in pregnant women with CH.

Methods: Cross-sectional study evaluating the effect of a standardized hydrotherapy session on AS in pregnant women with CH and controls. We used the device Mobil-O-Graph® NG to measure blood pressure (BP), heart rate (HR), and AS before and after a hydrotherapy session involving stretching, warming up, strengthening, and relaxation. The level of significance adopted in the statistical analyses was 5%.

Results: We evaluated 36 pregnant women, including 12 with hypertension (HG) and 24 controls (CG), aged 30.4 ± 4.8 years and at 29.2 ± 3.3 gestational weeks. Hydrotherapy promoted in both groups a significant reduction in AS assessed by the augmentation index at a HR of 75 bpm (AIx@75) (HG: 28.8 ± 7.3%, before; 22.4 ± 6.9%, after; p = 0.024; and CG: 29.1 ± 7.4%, before; 22.9 ± 6.6%, after; p = 0.001), as well as a reduction in HR (HG: 93.4 ± 11.8 bpm, before; 82.4 ± 10.0 bpm, after; p < 0.001; and CG: 91.4 ± 13.4 bpm, before; 81.5 ± 12.6 bpm, after; p < 0.001), but a nonsignificant reduction in BP.

Conclusion: We demonstrated that a hydrotherapy session acutely reduces AS assessed by AIx@75, and may represent a potential non-pharmacological strategy to prevent maternal and fetal complications in pregnant women with CH. (Arq Bras Cardiol. 2020; 114(4):647-654)

Keywords: Hypertension; Hydrotherapy; Pregnancy, High-Risk Ris/complications; Vascular Stiffness; Pre-Eclampsia.

Introduction

Hypertensive syndromes in pregnancy are associated with a higher risk of maternal and fetal complications. The various forms of hypertension during pregnancy cause about 14% of maternal deaths and are associated with dysfunctions affecting the newborn, such as low birth weight.[1,2] Several hypertensive syndromes occur during pregnancy, including preeclampsia, eclampsia, chronic hypertension, chronic hypertension with superimposed preeclampsia, and gestational hypertension.[3] Chronic hypertension (CH) causes 1 to 5% of all complications in pregnancy.[2]

In women with normotension or hypertension and in individuals in the general population, increased arterial stiffness (AS) has been recognized as a marker of higher risk for cardiovascular outcomes with even more significance than elevated peripheral blood pressure (BP) measured at the brachial artery (bBP).[4-6]

A portion of the pulse wave directed to the periphery is reflected back from peripheral impedance points. In healthy individuals, the reflected wave returns to the aorta during diastole. Due to aging or conditions that compromise arterial compliance, stiffer arteries reduce the transit time of incident and reflected waves. Consequently, reflected waves reach the aorta earlier, increasing central arterial pressures. The increased central pressure can be quantified by the augmentation index (Alx), defined as the percentage of central pulse pressure attributed to the reflected wave.[7] Evidence points out to Alx as a hallmark of the pathophysiology of hypertensive syndromes of pregnancy.[7] Increased Alx is recognized as a cardiovascular risk marker[5,7] and has been correlated with pregnancy complications, such as superimposed preeclampsia and fetal growth restriction, and a potentially additional future cardiovascular risk in women.[8-11]

Evidence shows a beneficial effect of regular physical activity in pregnant women with hypertension.[10,11] Aquatic physical therapy, better known as hydrotherapy, is a non-pharmacological intervention used in various clinical contexts that utilizes the properties of immersion in warm water associated with the practice of combined aerobic and resistance exercises.[12-17] However, no studies have evaluated the impact of this physical activity on AS in pregnant women with hypertension.

Mailing Address: Marcus Vinícius Bolívar Malachias •
Faculdade de Ciências Médicas de Minas Gerais, Alameda Ezequiel Dias, 275, Centro. Postal Code 30130-110, Belo Horizonte, MG – Brazil
E-mail: mbolivar@cardiol.br
Manuscript received January 25, 2018, revised manuscript May 05, 2019, accepted December 03, 2019

DOI: https://doi.org/10.36660/abc.20190055

In this study, we evaluated the acute effects of a standardized hydrotherapy session on AS parameters, such as AIx, in pregnant women with CH compared with a group of women with normal pregnancy. The analysis also included the heart rate (HR), systolic (SBP) and diastolic (DBP) BPs, mean BP (MBP), and peripheral (brachial artery) and central (aorta) pulse pressures (PPs).

Methods

Cross-sectional, controlled study conducted at the Aquatic Physical Therapy Clinic in Belo Horizonte (Minas Gerais, Brazil) from July 2015 to July 2016. The evaluation included 36 pregnant women, of whom 12 had chronic hypertension (thus considered to be at high risk) who were included in a hypertensive group (HG) and 24 normal-risk pregnant women who were included in a control group (CG). The diagnosis of hypertension during pregnancy was confirmed according to the 7th Brazilian Hypertension Guideline.[18] The study included high-risk and normal-risk pregnant women receiving prenatal care at Santa Casa de Belo Horizonte (MG), aged between 18 and 40 years, with a gestational age of 24 to 34 weeks, and with medical approval to perform aquatic activities, who were consecutively invited to participate in the research. Cases of multiple-gestation pregnancies, pregnant women who presented bleeding in the first and second pregnancy trimesters, smokers, and those with skin lesions or any condition that could be aggravated by immersion in heated water were excluded. The study was approved by the Research Ethics Committee of Faculdade Ciências Médicas de Minas Gerais, Brasil, (CEPCM-MG), under the opinion number 35487814.1.0000.5134. All pregnant women enrolled agreed to participate in the study and signed a free and informed consent form. For participation in the study, the group of pregnant women with hypertension should not interrupt or modify their pharmacological treatment, when previously prescribed, and during the research, these participants were encouraged to follow their health care recommendations.

Evaluation protocol

Initially, general data of the participants were collected, including age, gestational age, anthropometric measurements, personal medical history (clinical history of hypertension, diabetes mellitus, heart disease, chronic kidney disease, allergies, epilepsy), as well as information about exercise practice during pregnancy and medications in use. Vital signs of each participant were measured with the device Mobil-O-Graph® NG (IEM, Stolberg, Germany) before the participant was referred to the hydrotherapy session. After the session, clinical and hemodynamic parameters were measured once again.

Evaluation of blood pressure and arterial stiffness

Measurements of bBP, central blood pressure (cBP), and AS parameters were performed noninvasively using the Mobil-O-Graph® NG device (IEM, Stolberg, Germany) with the inbuilt ARC Solver algorithm (the ARC Solver Method, Austrian Institute of Technology). This device is an oscillometric monitor for ambulatory bBP measurement approved by the US Food and Drug Administration and the European *Conformité Européenne*, whose BP and AS detection unit has been validated by the British Hypertension Society and the American Heart Association's Council on Hypertension.[19-22] After measuring the upper limb perimeter and choosing the right cuff, measurements were carried out according to recommendations of the 7th Brazilian Guideline on Hypertension.[23] Three consecutive automated measurements were obtained, and the results were expressed as the average of the obtained values. AS was estimated by the variables AIx adjusted to a HR of 75 bpm (AIx@75) and pulse wave velocity (PWV). The equipment also provided measurements of HR, SBP, DBP, MBP, and peripheral and central PP.

Hydrotherapy session

Pregnant women from both groups, HG and CG, underwent standardized hydrotherapy sessions in a heated indoor pool with temperature between 32 and 34°C and duration of 40 minutes, with their bodies immersed up to the level of the xiphoid process.[24] Each session was divided into four 10-minute phases: stretching, warming up, strengthening, and relaxation. The first phase included three series of 30 seconds of stretching exercises of the anterior, posterior, and lateral trunk muscles. The second phase included a warm-up exercise consisting of walking at a comfortable speed based on self-assessment. The third phase consisted of upper and lower limb strengthening exercises. In the fourth phase, relaxation movements were performed.[24]

Statistical analysis

The analysis comprised the average of the three BP and AS measurements indicated by the device. Qualitative variables were presented as numbers and percentages, and quantitative variables as mean ± standard deviation. All continuous variables were subjected to the Shapiro-Wilk normality test. The comparison of means between two samples was performed by Student's *t* test; for differences in measurements before and after the intervention, the paired version was used, and for differences between groups, the version for independent samples was used. The analyses were performed using the software R, version 3.2.2 (R Foundation for Statistical Computing, Vienna, Austria). In the sample size calculated *a priori*, the significance level was set at 5% and the power at 90%, using a standard deviation of the differences in BP equal to 5.19 based on a similar previous study.[25] The detection of a difference of 5 required a total of 12 pregnant women with hypertension and 24 pregnant women in the control group, yielding a 2 to 1 ratio, the exact ratio used in our study.

Results

The sample of this study consisted of 36 pregnant women, of whom 24 (66.7%) were in the CG and 12 (33.3%) were in the HG group. The mean age was 30.4 ± 4.8 years, and the mean body mass index (BMI) was 31.7 ± 7.3 kg/m^2. At the time of the intervention, the participants' gestational age was 29.2 ± 3.3 weeks. Among the women participating in the study, 63.9% were black, 80.6% used some type of medication, and 22.2% practiced regular physical activities. There was no difference between the HG and CG in relation to race, physical activity, age, or gestational age. The HG had a higher mean BMI ($p < 0.001$) (Table 1).

Table 1 – Characteristics of the control (CG) and hypertensive (HG) groups

Variables	Entire sample (n = 36)	Control (n = 24)	Hypertensive (n = 12)	p
Age (years)	30.4 ± 4.8	30.5 ± 5.1	30 ± 4.3	0.741[T]
BMI (kg/m^2)	31.7 ± 7.3	28.1 ± 4.7	38.9 ± 6	< 0.001[T]
Race				0.719[F]
White	13 (36.1%)	8 (33.3%)	5 (41.7%)	
Black	23 (63.9%)	16 (66%)	7 (58.3%)	
Practice physical activity	8 (22.2%)	7 (29.2%)	1 (8.3%)	0.224[F]
Use of medications	29 (80.6%)	17 (70.8%)	12 (100%)	0.070[F]
Methyldopa	12 (41.4%)	-	12 (100%)	-
Multivitamin	11 (37.9%)	9 (52.9%)	2 (16.7%)	0.064[F]
Iron sulfate	6 (20.7%)	5 (29.4%)	1 (8.3%)	0.354[F]
Folic acid	4 (13.8%)	3 (17.6%)	1 (8.3%)	0.622[F]
Gestational age (weeks)	29.2 ± 3.3	29.3 ± 3.3	29 ± 3.5	0.840[T]

Note: The p values refer to Student's t test [T] for independent samples and Fisher's exact test [F]. BMI: body mass index.

Hydrotherapy promoted a significant reduction in AIx@75 in both groups, with percentage differences of 22.2% in the HG (p = 0.024) and 21.3% in the CG (p = 0.001), as shown in Figure 1. There was also a significant reduction in HR, with differences of 11 bpm (p < 0.001) in the HG and 9.9 bpm (p < 0.001) in the CG (Figure 2a). There was a trend toward a decrease in SBP after the hydrotherapy session, which was not significant (p = 0.050) (Figure 2b). There was no significant difference between the measurements obtained before and after the intervention for the other variables evaluated (Table 2).

In a comparison between the groups, higher values were observed in the HG compared with the CG regarding SBP, DBP, MAP, PP, central SBP, and PWV, both before and after the intervention (Table 2). However, there were no differences between groups in AIx@75 and HR values, which were variables that decreased significantly with the intervention.

No adverse events or discomforts associated with the hydrotherapy sessions were reported by the pregnant women evaluated.

Discussion

This study evaluated the impact of a hydrotherapy session on AS in high-risk pregnant women with CH compared with normal-risk pregnant women, yielding evidence unprecedented in the literature. Despite concerns about the safety of aquatic exercises during pregnancy, the procedure in our study proved to be safe for pregnant women with hypertension and controls in the third trimester of pregnancy. Barakat et al.[26] also demonstrated the safety of exercise practice among pregnant women. These authors compared the effects of exercise on pregnant women, concluding that while land exercises were more effective at preventing maternal weight gain, aquatic or combined programs involving land and water were more effective at preventing gestational diabetes.[26] Bacchi et al.,[27] evaluating 100 healthy pregnant women, concluded that three weekly sessions of aquatic activities during pregnancy prevent maternal overweight and preserve birth weight.

A meta-analysis concluded that a single isolated aerobic exercise session lasting 10 to 50 minutes at different intensities could reduce SBP by 5 to 7 mmHg, an effect that is maintained for up to 24 hours after training.[28] The magnitude of this reduction in SBP is comparable to the effect of most preferred antihypertensive drugs,[29] which presupposes a reduction in cardiovascular risk of 20 to 30%,[30] according to the conclusion of the position stand of the American College of Sports Medicine on exercise and hypertension.[31] In our study, we observed that hydrotherapy promoted a 6% reduction in SBP (139.6 ± 12.1 mmHg/130.1 ± 12.6 mmHg, p = 0.050) in the HG, a percentage similar to that described for other aerobic modalities but without a significant difference, probably due to the small sample size.

The BP variation in a liquid medium is considered to be predominantly affected by three components: temperature, immersion depth, and exercises during hydrotherapy.[32,33-35]

Small changes in water temperature have significant effects on heat loss or retention in the immersed patient because water has a thermal conductivity 25 times higher than air.[35] Additionally, the vasodilating effects of contact with heated water are well established.[36] The temperature of the water has a significant influence on maternal and fetal hemodynamics, and temperatures above 38.9°C have even been shown to cause potential embryonic or fetal deleterious effects.[37]

Despite using different parameters regarding the temperature of the water, duration, and level of immersion, there are reports of decreased BP induced by immersion.[38-40] Immersion causes reflex cardiovascular adjustments, such as redistribution of body fluids due to hydrostatic pressure, which leads to increased central blood volume, decreased HR, and increased systolic volume, cardiac output and natriuresis.[35]

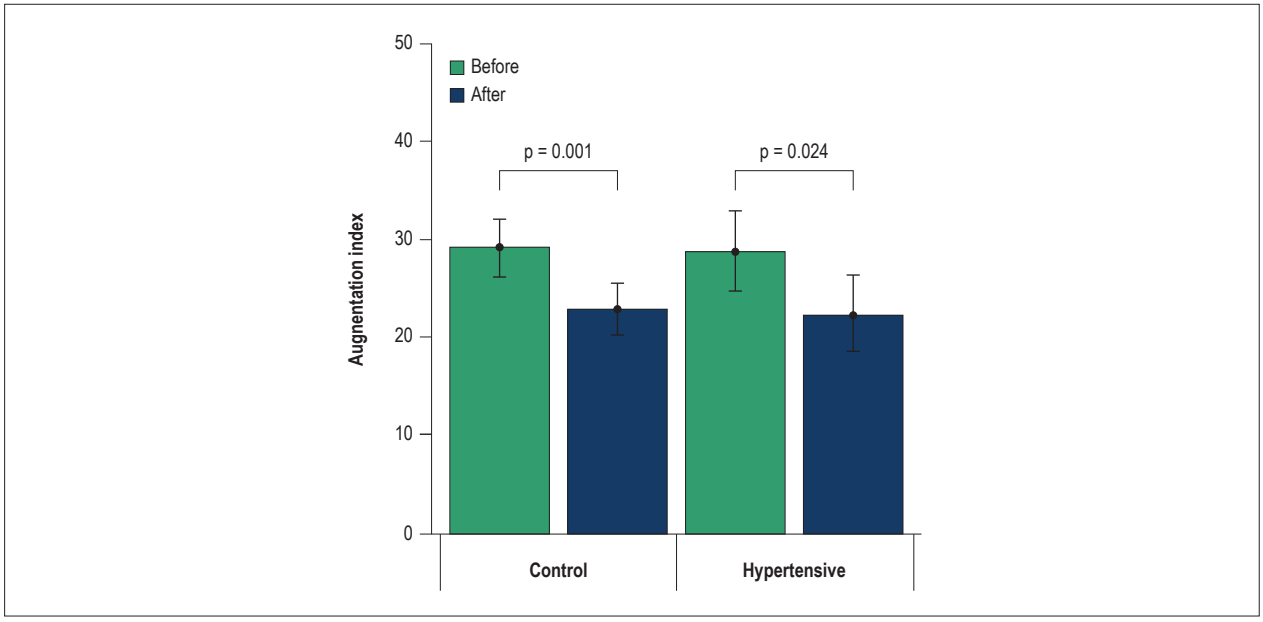


Figure 1 – *Reduction in the augmentation index adjusted for a heart rate of 75 bpm (AIx@75) (%) before and after a hydrotherapy session in the control (CG) and hypertensive (HG) groups.*

Table 2 – Longitudinal and intergroup comparison of the measures evaluated

Variables	Group	Before	After	P
Systolic blood pressure	Control	112 ± 7.6	110.8 ± 10.3	0.404
	Hypertensive	139.6 ± 12.1	130.1 ± 12.6	0.050
(mmHg)	P	< 0.001	< 0.001	
Diastolic blood pressure	Control	69.9 ± 6.9	70.1 ± 5.9	0.912
	Hypertensive	85.6 ± 9.9	82 ± 5.5	0.160
(mmHg)	P	< 0.001	< 0.001	
Mean blood pressure	Control	89.3 ± 6.5	88.7 ± 7.5	0.625
	Hypertensive	111.2 ± 9.6	103.5 ± 8.7	0.103
(mmHg)	P	< 0.001	< 0.001	
Pulse pressure	Control	41.6 ± 6.9	40.2 ± 7	0.320
	Hypertensive	53 ± 9.4	47.9 ± 10.2	0.190
(mmHg)	P	0.002	0.033	
Central systolic blood pressure	Control	102.9 ± 7.1	101.3 ± 9.3	0.276
	Hypertensive	126 ± 9.9	119.7 ± 8.9	0.161
(mmHg)	P	< 0.001	< 0.001	
Heart rate	Control	91.4 ± 13.4	81.5 ± 12.6	< 0.001
	Hypertensive	93.4 ± 11.8	82.4 ± 10.0	< 0.001
(bpm)	P	0.650	0.819	
PWV	Control	5.1 ± 0.3	5.1 ± 0.4	0.469
	Hypertensive	6 ± 0.4	5.8 ± 0.5	0.151
	P	< 0.001	0.001	
AIx@75 (%)	Control	29.1 ± 7.4	22.9 ± 6.6	0.001
	Hypertensive	28.8 ± 7.3	22.4 ± 6.9	0.024
	P	0.903	0.852	

Note: The p values refer to Student's t test for paired samples in the columns and independent samples in the rows. PWV: pulse wave velocity (m/s); AIx@75: augmentation index adjusted for the heart rate of 75 bpm in %.

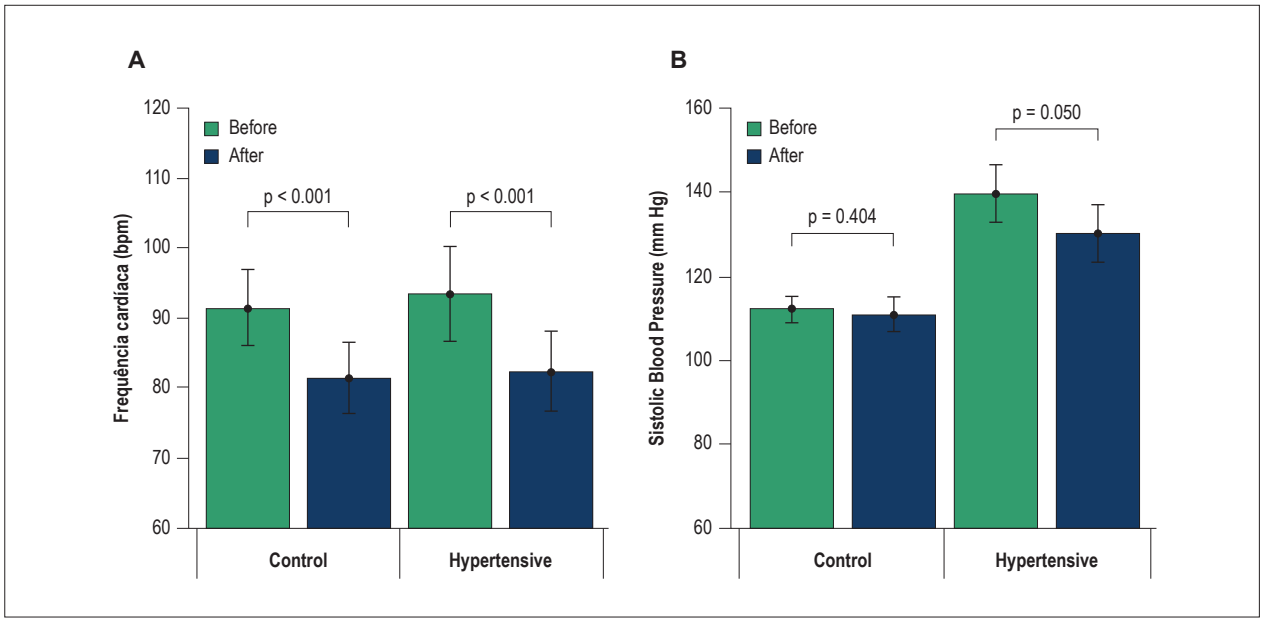


Figure 2 – *Variations in heart rate (A) and brachial (peripheral) systolic blood pressure (B) before and after a hydrotherapy session in the control (CG) and hypertensive (HG) groups.*

Finkelstein et al.[41] found a significant reduction in HR and BP among pregnant women immersed up to the level of the xiphoid process, as done in our study. The authors suggest that this decrease may be related to decreased plasma renin activity and increased atrial natriuretic peptide concentration in response to blood volume expansion in water. Elvan-Taşpınar et al.[42] compared the effect on central and peripheral hemodynamics of simple immersion in water at 35°C for 3 hours in a small sample divided into 3 groups: normal-risk pregnant women, pregnant women with preeclampsia, and nonpregnant women. The authors observed a transient reduction in HR, DBP, and total peripheral resistance.[42]

Still, there is evidence that exercise produces a significant additional cardiovascular impact during pregnancy and in other clinical conditions.[36,43-45] In a study by Ward et al.[25] evaluating the impact of aquatic physical therapy in normotensive pregnant women, no significant changes in post-immersion BP compared with pre-immersion BP were observed; however, a significant reduction in MBP in the post-exercise phase was noted. Coelho et al.[45] demonstrated a significant reduction in SBP, DBP, and MBP among pregnant women without hypertension 45 and 60 minutes after an aquatic exercise session.

We conclude that there is sufficient evidence showing that aquatic physical therapy promotes an impact on BP components through an interaction of the effects of its three fundamental elements: temperature, immersion, and exercise. Although still an area with limited research, these studies demonstrated the effects of hydrotherapy on BP in normal individuals, pregnant or not, opening up to possibilities of intervention in hypertensive pregnant women. However, there is no previous evidence in the literature about the impact of hydrotherapy on AS in pregnant women with CH, a parameter evaluated in our study.

Measurements of AS, such as the ones expressed by AIx@75, as well as central SBP (cSBP), have been shown to be more sensitive independent predictors of future cardiovascular events compared with conventional bBP in various clinical conditions[46-49] and in pregnancy.[50,51] The AIx@75 has been shown to be independent of bBP during pregnancy, indicating that the AIx@75 measurement may reflect arterial compliance during pregnancy.[50] A close inverse association between the newborn's birth weight and AS of normotensive pregnant women has also been demonstrated, indicating that abnormal pressure-wave reflection may affect fetal growth even in the absence of hypertension.[51] Additionally, increased AIx@75 and cSBP have been observed in women with newly diagnosed preeclampsia.[52] Khalil et al.[9] demonstrated a change in pressure-wave reflection after the first trimester of pregnancy in women developing preeclampsia. Yinon et al.[10] demonstrated increased AIx@75 percentages up to 6 to 24 months after delivery in pregnant women with a history of intrauterine growth restriction and/or early-onset preeclampsia. Tomimatsu et al.[53] showed that abnormal pressure-wave reflection during the 26 to 32 gestational weeks correlated more strongly with birth weight than conventional bBP, to the extent that AIx@75 was the only hemodynamic parameter significantly elevated in pregnant women who developed fetal growth restriction. Such evidence corroborates our findings of decreased AIx@75 without significant bSBP reduction with hydrotherapy. We demonstrated in our study that a single hydrotherapy session was able to decrease AIx@75 acutely by 22.2% and 21.3% in pregnant women with CH and controls, respectively. The intervention proved to be safe and may represent a potential non-pharmacological therapeutic strategy for pregnant women with CH in preventing maternal and fetal complications.

Conclusion

In a pioneering study, we demonstrated that a hydrotherapy session is able to promote a reduction in AS assessed by AIx@75 in high-risk pregnant women with CH in the third trimester of pregnancy.

Limitations

Our study has potential limitations. The number of patients evaluated was relatively small, even though it respected the sample size calculated *a priori* for a proper evaluation of the hypothesis. Also, we recognize that the study was conducted at a single center and, for greater sample homogeneity, was restricted to the gestational period of 24 to 34 weeks; therefore, it may not represent the entire universe of pregnant women with CH. We only evaluated the acute effect of a single hydrotherapy session; however, being safe and potentially beneficial, there is a promising possibility of amplification of these initial results if the intervention is performed more continuously in this patient population. We hope that similar research can be conducted in a larger number of patients of different ethnic and social characteristics and in other locations to replicate and broaden our findings.

Author contributions

Conception and design of the research, acquisition of data analysis and interpretation of the data: Linhares GM, Machado AV, Malachias MVB; statistical analysis, writing of the manuscript and critical revision of the manuscript for intellectual content: Linhares GM, Malachias MVB.

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 Giovana Macêdo Linhares, from Faculdade de de Ciências Médicas de Minas Gerais/Fundação Educacional Lucas Machado.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Faculdade de de Ciências Médicas de Minas Gerais under the protocol number 35487814.1.000.5134 . 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.

References

1. Say L, Chou D, Gemmill A, Tunçalp Ö, Moller AB, Daniels J, et al. Global causes of maternal death: a WHO systematic analysis. Lancet Glob Health. 2014;2(6):323-33.
2. Bramham K, Parnell B, Nelson-Piercy C, Seed PT, Poston L, et al. Chronic hypertension and pregnancy outcomes: systematic review and meta-analysis. BMJ. 2014 Apr 15;348:g2301.
3. Roberts JM, August PA, Bakris G, Barton JR, Bernstein IM, Druzin M, et al. Hypertension in pregnancy. Report of the American College of Obstetricians and Gynecologists' Task Force on Hypertension in Pregnancy. Obstet Gynecol. 2013;122(5):1122-31.
4. Seeland U, Brecht A, Nauman AT, Oertelt-Prigione S, Ruecke M, Knebel F, et al. Prevalence of arterial stiffness and the risk of myocardial diastolic dysfunction in women. Biosci Rep. 2016;36(5):pii:e00400.
5. Manisty C, Mayet J, Tapp RJ, Parker KH, Sever P, Poulter NR, et al. Wave reflection predicts cardiovascular events in hypertensive individuals independent of blood pressure and other cardiovascular risk factors: an ASCOT (Anglo-Scandinavian Cardiac Outcome Trial) substudy. J Am Coll Cardiol. 2010;56(1):24-30.
6. Patvardhan E, Heffernan KS, Ruan J, Hession M, Warner P, Karas RH,et al. Augmentation index derived from peripheral arterial tonometry correlates with cardiovascular risk factors. Cardiol Res Pract. 2011;2011:253758.
7. Fukushima T, Eguchi K, Ohkuchi A, Miyashita H, Kario K. Changes in central hemodynamics in women with hypertensive pregnancy between before and after delivery. J Clin Hypertens. 2016;18(4):329-36.
8. Franz MB, Burgmann M, Neubauer A, Zeisler H, Sanani R, Gottsauner-Wolf M, et al. Augmentation index and pulse wave velocity in normotensive and pre-eclamptic pregnancies. Acta Obstet Gynecol Scand. 2013;92(8):960-6.
9. Khalil A, Cowans NJ, Spencer K, Goichman S, Meiri H, Harrington K. First-trimester markers for the prediction of pre-eclampsia in women with a-priori high risk. Ultrasound Obstet Gynecol. 2010;35(6):671-9.
10. Yinon Y, Kingdom JC, Odutayo A, Moineddin R, Drewlo S, Lai V, et al. Vascular dysfunction in women with a history of preeclampsia and intrauterine growth restriction: insights into future vascular risk. Circulation. 2010;122(18):1846-53.
11. Thompson EL, Vamos CA, Daley EM. Physical activity during pregnancy and the role of theory in promoting positive behavior change: a systematic review. J Sport Health Sci. 2017;6(2):198-206.
12. Magro-Malosso ER, Saccone G, Di Tommaso M, Roman A, Berghella V. Exercise during pregnancy and risk of gestational hypertensive disorders: a systematic review and meta-analysis. Acta Obstet Gynecol Scand. 2017;96(8):921-31.
13. Mooventhan A, Nivethitha L. Scientific evidence-based effects of hydrotherapy on various systems of the body. N Am J Med Sci. 2014;6(5):199-209.
14. Depiazzi JE, Forbes RA, Gibson N, Smith NL, Wilson AC, Boyd RN, et al. The effect of aquatic high-intensity interval training on aerobic performance, strength and body composition in a non-athletic population: systematic review and meta-analysis. Clin Rehabil. 2019;33(2):157-70.
15. Moreira OC, Lopes GS, de Matos DG Mazini-Filho ML, Aidar FJ, Silva SF, et al. Impact of two hydrogymnastics class methodologies on the functional capacity and flexibility of elderly women. J Sports Med Phys Fitness. 2019;59(1):126-31.
16. Sujan MU, Rao MR, Kisan R, Abhishekh HA, Nalini A, Raju TR, et al. Influence of hydrotherapy on clinical and cardiac autonomic function in migraine patients. J Neurosci Rural Pract. 2016;7(1):109-13.

17. Kasawara KT, Nascimento SL, Costa ML, Surita FG, e Silva JL. Exercise and physical activity in the prevention of pre-eclampsia: systematic review. Acta Obstet Gynecol Scand. 2012;91(10):1147-57.

18. Malachias MVB, Figueiredo CEP, Sass N, Antonello IC, Torloni MR, Bortolotto MRFL. 7th Brazilian Guideline of Arterial Hypertension: Chapter 9 - Arterial Hypertension in pregnancy. Arq Bras Cardiol. 2016;107(3 Suppl 3):49-52.

19. Hametner B, Wassertheurer S, Kropf J, Mayer C, Eber B, Weber T. Oscillometric estimation of aortic pulse wave velocity: comparison with intra-aortic catheter measurements. Blood Press Monit. 2013;18(3):173-6.

20. Weber T, Wassertheurer S, Rammer M, Maurer E, Hametner B, Mayer CC, et al. Validation of a brachial cuff-based method for estimating central systolic blood pressure. Hypertension. 2011;58(5):825-32.

21. Nunan D, Wassertheurer S, Lasserson D, Hametner B, Fleming S, Ward A, et al. Assessment of central haemomodynamics from a brachial cuff in a community setting. BMC Cardiovasc Disord. 2012 Jun 26;12:48.

22. Weiss W, Gohlisch C, Harsch-Gladisch C, Tölle M, Zidek W, van der Giet M. Oscillometric estimation of central blood pressure: validation of the Mobil-O-Graph in comparison with the SphygmoCor device. Blood Press Monit. 2012;17(3):128-31.

23. Malachias MVB, Gomes MAM, Nobre F, Alessi A, Feitosa AD, Coelho EB. 7th Brazilian Guideline of Arterial Hypertension: Chapter 2 - Diagnosis and Classification. Arq Bras Cardiol. 2016;107(3 Suppl 3):7-13.

24. Ruoti RG, Morris DM, Cole AJ. Reabilitação aquática. São Paulo: Manole; 2000. 463p.

25. Ward EJ, McIntyre A, Kessel GV, Hague WM. Immediate blood pressure changes and aquatic physiotherapy. Hypertens Pregnancy. 2005;24(2):93-102.

26. Barakat R, Perales M, Cordero Y, Bacchi M, Mottola MF. Influence of land or water exercise in pregnancy on outcomes: a cross-sectional study. Med Sci Sports Exerc. 2017;49(7):1397-1403.

27. Bacchi M, Mottola FM, Perales M, Refoyo I, Barakat R. Aquatic activities during pregnancy prevent excessive maternal weight gain and preserve birth weight: a randomized clinical trial. Am J Health Promot. 2018;32(3):729-35.

28. Cornelissen VA, Smart NA. Exercise training for blood pressure: a systematic review and meta-analysis. J Am Heart Assoc. 2013;2(1):e004473.

29. ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid- Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2002;288(23):2981-97.

30. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. Ann Intern Med. 2002;136(7):493-503.

31. Pescatello LS, Franklin BA, Fagard R, Farquhar WB, Kelley GA, Ray CA, et al. American College of Sports Medicine position stand. Exercise and hypertension. Med Sci Sports Exerc. 2004;36(3):533-53.

32. Barbosa TM, Garrido MF, Bragada J. Physiological adaptations to head-out aquatic exercise with different levels of body immersion. J Strength Cond Res. 2007;21(4):1255-9.

33. Alberton CA, Kruel LFM. Influence of immersion on resting cardiorespiratory responses.. Rev Bras Med Esporte. 2009;15(3):228-32.

34. Becker BE. Aquatic therapy: scientific foundations and clinical rehabilitation applications. Physical Medical Reahabilitation. 2009;1(9):859-72.

35. Katz VL, McMurray R, Cefalo RC. Aquatic exercise during pregnancy. In: Mittelmark RA, Wiswell RA, Drinkwater BL, eds. Exercise in Pregnancy. 2nd ed. Baltimore: Williams and Wilkins; 1991.

36. Soultanakis HN. Aquatic exercise and thermoregulation in pregnancy. Clin Obstet Gynecol. 2016;59(3):576-90.

37. Rogers J, Davis BA. How risky are hot tubs and saunas for pregnant women? MCN Am J Matern Child Nurs. 1995;20(3):137-40.

38. Katz VL, Rozas L, Ryder R, Cefalo RC. Effect of daily immersion on the edema of pregnancy. Am J Perinatol. 1992;9(4):225-7.

39. Doniec-Ulman I, Kokot E, Wambach G, Drab M. Water immersion-induced endocrine alterations in women with Eph gestosis. Clin Nephrol. 1987;28(2):51-5.

40. Kokot F, Ulman J, Cekanski A. Influence of head out water immersion on plasma renin activity, aldosterone, vasopressin and blood pressure in late pregnancy toxaemia. Proc Eur Dial Transplant Assoc. 1983;20:557-61.

41. Finkelstein I, Alberton CL, Figueiredo PAP, Garcia DR, Tartaruga LAP, Kruel LFM. Behavior of heart rate, blood pressure, and hydrostatic weight of pregnant women at different immersion depths.. Rev Bras Ginecol Obstet. 2004;26(9):685-90.

42. Elvan-Taspınar A, Franx A, Delprat CC, Bruinse HW, Koomans HA. Water immersion in preeclampsia. Am J Obstet Gynecol. 2006;195(6):1590-5.

43. Bacchi M, Mottola FM, Perales M, Refoyo I, Barakat R. Aquatic activities during pregnancy prevent excessive maternal weight gain and preserve birth weight: a randomized clinical trial. Am J Health Promot. 2018;32(3):729-35.

44. Barbosa TM, Garrido MF, Bragada J. Physiological adaptations to head-out aquatic exercise with different levels of body immersion. J Strength Cond Res. 2007;21(4):1255-9.

45. Coelho BT, Polito MD, Efeito agudo de uma sessão de hidroginastica sobre a resposta da pressão arterial em gestantes não hipertensas. Rev SOCERJ.2009;22(2):75-9.

46. The CAFE Investigators, CAFE Steering Committee and Writing Committee, Williams B, Lacy PS, Thom SM, Cruickshank K, et al. Differential impact of blood pressure-lowering drugs on central aortic pressure and clinical outcomes: principal results of the Conduit Artery Function Evaluation (CAFE) study. Circulation. 2006;113(9):1213-25.

47. Roman MJ, Devereux RB, Kizer JR, Lee ET, Galloway JM, Ali T, et al. Central pressure more strongly relates to vascular disease and outcome than does brachial pressure: the Strong Heart Study. Hypertension. 2007;50(1):197-203.

48. Chirinos JA, Zambrano JP, Chakko S, Veerani A, Schob A, Willens HJ, et al. Aortic pressure augmentation predicts adverse cardiovascular events in patients with established coronary artery disease. Hypertension. 2005;45(5):980-5.

49. London GM, Blacher J, Pannier B, Guérin AP, Marchais SJ, Safar ME. Arterial wave reflections and survival in end-stage renal failure. Hypertension. 2001;38(3):434-8.

50. Fujime M, Tomimatsu T, Okaue Y, Koyama S, Kanagawa T, Taniguchi T, et al. Central aortic blood pressure and augmentation index during normal pregnancy. Hypertens Res. 2012;35(6):633-8.

51. Tomimatsu T, Fujime M, Kanayama T, Mimura K, Koyama S, Kanagawa T, et al. Maternal arterial stiffness in normotensive pregnant women who subsequently deliver babies that are small for gestational age. Eur J Obstet Gynecol Reprod Biol. 2013;169(1):24-7.

52. Khalil A, Jauniaux E, Harrington K. Antihypertensive therapy and central hemodynamics in women with hypertensive disorders in pregnancy. Obstet Gynecol. 2009;113(3):646-54.

53. Tomimatsu T, Fujime M, Kanayama T, Mimura K, Koyama S, Kanagawa T, et al. Abnormal pressure-wave reflection in pregnant women with chronic hypertension: association with maternal and fetal outcomes. Hypertens Res. 2014;37(11):989-92.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Short Editorial: Hydrotherapy Reduces Arterial Stiffness in Pregnant Women with Chronic Hypertension

Celso Amodeo

Universidade Federal de São Paulo (UNIFESP), São Paulo, SP – Brazil

Increased pulse pressure is associated with aging. This is mainly caused by increased systolic pressure, but also by decreased diastolic pressure. Diastolic blood pressure below 50 mmHg has been related to increased cardiovascular risk.

With the development of devices that allow the indirect estimation of central pressure from the aortic root and analysis of arterial stiffness (another marker of cardiovascular risk), many studies have shown that changes in vascular dynamics are detected earlier using central measurements compared with peripheral blood pressure measurements.

Assessment of pulse wave velocity allows the analysis of arterial stiffness and determination of the augmentation index, which corrected by the heart rate of 75 bpm (AIx@75), is associated with greater arterial stiffness and higher cardiovascular risk.

The study by Linhares et al.[1] reports the results of central pressure measurements in pregnant women with and without hypertension undergoing hydrotherapy. This is an interesting study considering that the pathophysiology of preeclampsia and eclampsia is still on debate. Some authors have reported different behaviors of these central blood pressure parameters in normal pregnancy and in women with eclampsia/preeclampsia.

In the discussion section, the authors cited the study by Yinon et al.[2] who observed an increased AIx@75 in women with previous early-onset preeclampsia and intrauterine growth restriction. Tomimatsu et al.[3] also reported that an AIx@75 measured during 26–32 weeks of gestation showed a stronger correlation with birth weight than brachial blood pressure, indicating that the AIx@75 is a relevant hemodynamic parameter in pregnant women with intrauterine growth restriction.

From this information, Linhares et al. investigated the effects of hydrotherapy on central blood pressure parameters, central systolic and diastolic blood pressure, AIx@75 and pulse wave velocity in pregnant women. The authors observed the behavior of arterial stiffness in response to hydrotherapy. The acute effect of the therapy was a reduction in AIx@75 in both hypertensive and normotensive pregnant women, but no changes were seen in pulse wave velocity or brachial blood pressure. The authors did not evaluate, however, the duration of AIx@75 reduction, and whether this effect would have an impact on preventing hypertensive complications in pregnancy. This opens the possibility for future studies on the pathophysiological mechanisms of preeclampsia and eclampsia. Also, the results indicate the use of hydrotherapy as an instrument for early detection of pregnant women at risk for development of hypertensive complications.

References

1. Linhares GM, Machado AV, Malachias MVB. A hiroterapia reduz a rigidez arterial em gestantes hipertensas crônicas. Arq Bras Cardiol. 2020; 114(4):647-654
2. Yinon Y, Kingdom JC, Odutayo A, Moineddin R, Drewlo S, Lai V, et al. Vascular dysfunction in women with a history of preeclampsia and intrauterine growth restriction: insights into future vascular risk. Circulation. 2010;122(18):1846-53.
3. Tomimatsu T, Fujime M, Kanayama T, Mimura K, Koyama S, Kanagawa T, et al. Abnormal pressure-wave reflection in pregnant women with chronic hypertension: association with maternal and fetal outcomes. Hypertens Res. 2014;37(11):989-92.

keywords

Pregnant Women/complicações; Hypertension; Pre-Eclampsia; Pulse Wave Analysis; Blood Pressure; Vascular Stiffness; Hydrotherapy/methods

Mailing Address: Celso Amodeo •
Rua Abilio Soares, 233 cjto 51. Postal Code 04005-000,
Paraíso, SP - Brazil
E-mail: camodeo@terra.com.br

DOI: https://doi.org/10.36660/abc.20200251

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Controlled Study of Central Hemodynamic Changes in Inspiratory Exercise with Different Loads in Heart Failure

Luana de Decco Marchese,[1,2] Sergio Chermont,[1,3] Danielle Warol,[1] Lucia Brandão de Oliveira,[2] Sabrina Bernardez Pereira,[4] Mônica Quintão,[1,5] Evandro Tinoco Mesquita[1]

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

Centro Universitário Serra dos Órgãos – Clínica de Insuficiência Cardíaca (CLIC),[2] Teresópolis, RJ – Brazil

Hospital Santa Martha,[3] Niterói, RJ – Brazil

Hospital do Coração,[4] São Paulo, SP – Brazil

Instituto Nacional do Câncer,[5] Rio de Janeiro, RJ – Brazil

Abstract

Background: Inspiratory muscle weakness contributes to exercise intolerance and decreased quality of life in patients with heart failure. Studies with inspiratory muscle training show improvement in inspiratory muscle strength, functional capacity and quality of life. However, little is known about the central hemodynamic response (CHR) during inspiratory exercise (IE).

Objective: To evaluate CHR in a single IE session with different loads (placebo, 30% and 60%) in heart failure.

Methods: Randomized placebo-controlled clinical trial in patients with heart failure with reduced ejection fraction, functional class II and III. Twenty patients aged 65 ± 11 years completed a single session of inspiratory exercise, in 3 cycles of 15 minutes, with a 1-hour washout, involving loads of 30% (C30), 60% (C60) and placebo, using a linear load resistor (PowerBreathe Light). The noninvasive hemodynamic study was performed by cardiothoracic bioimpedance (Niccomo™ CardioScreen®). Statistical analysis was performed with Student's t-test and Pearson's correlation, and P≤0.05 was considered significant.

Results: An increase in heart rate (HR) was observed with C30 (64 ± 15 vs 69 ± 15 bpm; p = 0.005) and C60 (67 ± 14 vs 73 ± 14 bpm, p = 0.002). A decrease was observed in systolic volume (SV) with C30 (73 ± 26 vs 64 ± 20 ml; p = 0.004). Cardiac output (CO), on its turn, increased only with C60 (4.6 ± 1.5 vs 5.3 ± 1.7 l/min; p = -0.001).

Conclusion: When using the 60% load, in a single IE session, changes in CHR were observed. HR and CD increased, as did the Borg scales and subjective sensation of dyspnea. The 30% load reduced the SV. (Arq Bras Cardiol. 2020; 114(4):656-663)

Keywords: Heart Failure; Muscle Weaknerss; Breathing Exercises; Hemodynamics; Fatigue Syndrome, Chronic; Fatigue Syndrome, Chronic; Quality of Life; Exercise Therapy; Exercise Movement Techniques.

Introduction

Most patients with heart failure (HF) have exercise intolerance, mainly due to symptoms such as dyspnea and fatigue. This low tolerance to physical efforts generates a cycle of physical inactivity and a consequent decrease in quality of life.[1]

In addition to other mechanisms previously described such as excessive ventilatory need, exacerbated muscle ergoreflex and increased sympathetic activity, inspiratory muscle weakness, present in approximately 30 to 50% of patients with heart failure with reduced ejection fraction (HFREF), has been identified as a factor that can contribute to exercise intolerance[2,3] and has an independent prognostic value.[4,5]

Previous studies have shown that inspiratory muscle training (IMT) results in significant improvements in inspiratory muscle strength, functional capacity, dyspnea and ventilatory response during exercise, besides contributing to the improvement in quality of life of patients with HF.[6,7] However, the ideal training intensity to optimize these results is still unclear. A recent systematic review with meta-analysis suggested that high-intensity IMT is superior to lower loads and does not appear to have any adverse effects.[8]

Most studies have focused on demonstrating the systemic benefits of IMT, but little is known about the central hemodynamic response (CHR) of these patients during inspiratory exercise (IE).[9] The hypothesis of the present study is that, with higher loads, greater hemodynamic repercussions

Mailing Address: Luana de Decco Marchese •
Centro Universitário Serra dos Órgãos - Av. Delfim Moreira, 2799. Postal Code 25964-000, Vale do Paraíso, Teresópolis, RJ – Brazil
E-mail: luana_dmarchese@hotmail.com
Manuscript received November 23, 2018, revised manuscript February 05, 2019, accepted June 05, 2019

DOI: https://doi.org/10.36660/abc.20180375

would be observed. Therefore, this study aimed to assess CHR in a single session of inspiratory exercise with different loads (placebo, 30 and 60%) in HFREF.

Methods

Randomized, placebo-controlled clinical trial. The load was placed on the linear load resistor, in a way that participants could not see at which level the marker was positioned and were also not informed about the load used.

Inclusion and exclusion criteria

To meet the objective of this study, 29 patients with HFREF from the Heart Failure Clinic (CLIC) of *Centro Universitário Serra dos Órgãos* (UNIFESO) were selected. They all met the following inclusion criteria: clinical diagnosis of heart failure, age over 21 years, Doppler echocardiogram with left ventricular ejection fraction (LVEF) <45% (Simpson method), class II and III by the New York Heart Association (NYHA), stable disease for at least three months, never having undergone or not being treated with IMT. None of the following exclusion criteria were present: clinical (medical) diagnosis of chronic obstructive pulmonary disease, unstable angina, major cardiac arrhythmias, acute myocardial infarction in the last three months, inability to perform the IE session. And yet none of the exclusion criteria for cardiothoracic bioimpedance: massive pleural effusion, anasarca, moderate or severe aortic insufficiency, use of intra-aortic balloon, mean arterial pressure >130mmHg, height <1.20m or >2.30m, weight <30kg or >155kg, and use of pacemakers with sensors to adjust heart rate according to respiratory rate.

Assessment methods

Collection instruments used were: an analogue manovacuometer (Critical Med®, Brazil), a linear load resistor (PowerBreathe Light®, United States), and a cardiothoracic bioimpedance (CTB) device (Niccomo™ CardioScreen®, Germany).

The inspiratory muscle exercise (IME) sessions were performed according to the randomization made by the Randomizer website, using the linear load resistor for 15 minutes with the following loads: 0 (placebo), 30% and 60% of the maximum inspiratory pressure (MIP) value measured previously by manovacuometry, with a 1-hour washout. To monitor the hemodynamic repercussions, the CTB device was used.

Inspiratory exercise

As this was the first time participants used the linear load resistor, after the initial evaluation they were instructed on how to perform the IE and then remained at rest for 15 minutes before beginning hemodynamic monitoring.

Following the load randomization done previously (placebo, 30% or 60%), the IE was performed for 15 minutes, with the patient in supine position on a reclining chair, at 45º of elevation. All participants used the same linear load resistor, but an individual filter from the same manufacturer was used and discarded after the experiment.

Throughout the IE, the patient was instructed to perform inspiration and expiration according to the sound signal emitted by a software (Paced Breathing), so all participants performed 15 breaths per minute.[8] The sessions with the other loads were carried out after a one-hour interval between each. For the IE with placebo, the device's spring was removed, only the unidirectional valve was left, therefore no resistance was present to the patient's inspiration.

Statistical analysis

The appropriate number of participants to be studied was calculated based on previous publications that showed which intervention, such as the effects of exercise, caused significant changes, such as increased heart rate, among others. For this magnitude of effects and to set statistical power at 0.8 and alpha error at 0.05, the sample should be comprised of 20 individuals.

All data were subjected to Kolmogorov-Smirnov analysis to determine whether or not there was a normal distribution of the sample and data. Hemodynamic variables during IE, in Placebo, 30% or 60% groups, were compared using the Student's t test for paired variables. For the association of independent variables, Pearson's correlation was used. When p values were significant, paired comparisons were made using the Bonferroni test (post-hoc).

The data were transferred to a systematic spreadsheet in Prism GraphPad 5.0 software (GraphPad Software, San Diego, CA). Categorical variables were expressed as absolute numbers. All results were expressed as mean±standard deviation and p values <0.05 were considered statistically significant.

Ethical considerations

All participants in this study received detailed information about the purpose of the research and the procedures to be performed. The protocol was sent to UNIFESO's Research Ethics Committee and approved under opinion number 420.737, registered at *Plataforma Brasil*.

Before taking part in the study, all participants signed the informed consent form, according to resolution 466/2012 of the National Health Council.

Results

Among the 29 participants selected for the study, 20 completed the experiment (9 patients refused to participate) (Figure 1). Table 1 describes the demographic, clinical and pharmacological treatment characteristics of the sample.

Responses of central hemodynamic variables to IE

The central hemodynamic response had a different behavior according to different IE loads in our sample. HR increased with loads of 30% (C30) (64 ± 15 vs 69 ± 15 bpm; p=0.005) and

60% (C60) (67 ± 14 vs 73 ± 14 bpm, p=0.002), but did not change in the placebo mode (P) (Figure 2). There was a decrease in SV when the IE was performed with C30 (73 ± 26 vs 64 ± 20 ml; p=0.004) and there were no changes with placebo and C60 (Figure 3). The DO increased when the IE was performed on C60 (4.6 ± 1.5 vs 5.3 ± 1.7 l/min; p=-0.001) and did not change with placebo and C30 (Figure 4).

Responses of other hemodynamic variables to IE

In addition to CHR, other hemodynamic variables also changed along the IE on the load C60. Placebo and C30 did not cause any changes in the variables presented.

When the IE was performed on C60, there was an increase in systolic blood pressure (SBP) (124.1 ± 27.4 vs 130.6 ± 25.9 mmHg; p=0.001) (Figure 5), mean arterial pressure (MAP) (85.7 ± 17.9 vs 89.2 ± 17.3 mmHg, p=0.004) (Figure 6), as well as an increase in Borg scale of perceived exertion (0.3±0.9 vs 1.1±1.9, p=0.01) (Figure 7) and the subjective dyspnea scale (0.2±0.7 vs 0.8±1.5, p=0.02) (Figure 8).

Correlation

There was a moderate correlation between baseline CO and inspiratory muscle strength (r=0.45; p=0.04) (Figure 9).

Discussion

This is a pioneer study in describing changes in CHR with different IE loads in outpatients with HFREF, using a non-invasive method of hemodynamic monitoring. Different IMT strategies are used in clinical practice, but it is not clear which training intensity is the most efficient.

There were different hemodynamic behaviors when comparing placebo, 30% and 60% loads. Only the HR showed a similar response to IE with both loads of 30% and 60%, being increases. SV, on the other hand, had a significant drop only when the 30% load was used, and the CO increased only with the highest load, 60%. The control group (placebo) showed no significant change.

In this study, the hypothesis that different IE loads could produce different central hemodynamic responses was tested. Although both HR[10] variability and the effects of respiratory muscle fatigue[11] after IMT have already been

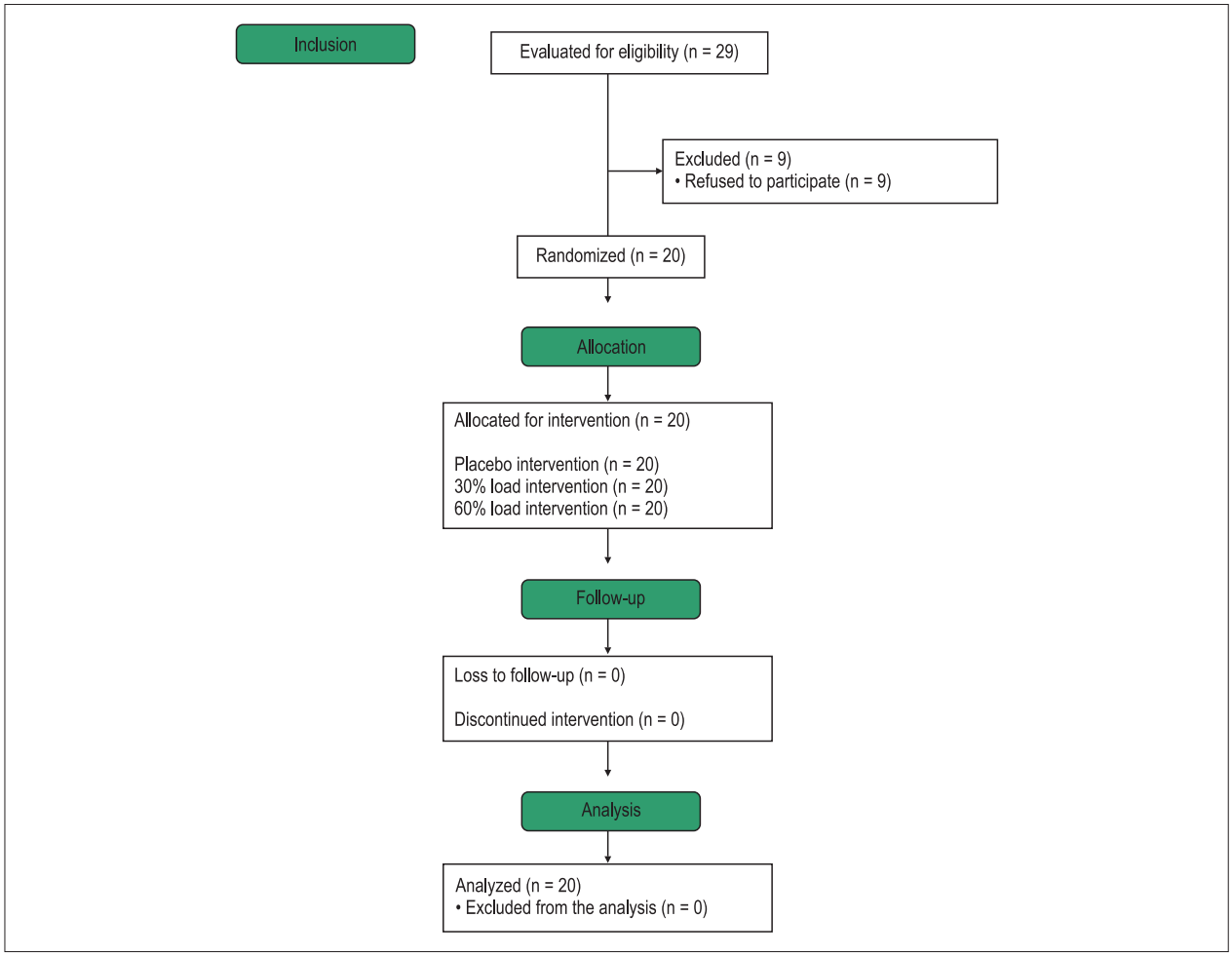


Figure 1 – *CONSORT flowchart.*

Table 1 – Sample characteristics

	n=20
Gender	13M\7F
Age (years)	65 ± 11
Weight (kg)	72 ± 14
Height (cm)	164 ± 11
BMI (kg/m2)	26.7 ± 4.4
Ethnicity	Caucasian (7). Brown (6). Afrodescendants (7)
NYHA	Class II (14). Class III (6)
LVEF (%)	37.2 ± 6.3
MIP (cm\H2O)	- 101 ± - 43
MEP (cm\H2O)	95 ± 42
30% load IMT (cm\H2O)	31 ± 11
60% load IMT (cm\H2O)	61 ± 25
Pharmacological therapy	
ACE inhibitor, %	55
Diuretics, %	75
β-blocker, %	80

M: male; F: female; kg: kilogram; cm: centimeters; BMI: body mass index; kg/m²: kilograms per square meter; LVEF: left ventricular ejection fraction; MIP: maximum inspiratory pressure; MEP: maximal expiratory pressure; IMT: inspiratory muscle training; cm/H_2O: centimeters of water; ACE: angiotensin-converting enzyme.

tested, this study, until then, is the only one to verify the central hemodynamic response of different IE loads in patients with HFREF.

To assess hemodynamic response, a cardiothoracic bioimpedance device was used, which is a noninvasive hemodynamic assessment method that, when compared to thermodilution methods, showed high correlation.[12] Even when used to assess cardiac patients, as shown in the study by Villacorta et al.,[13] CTB showed accuracy in the calculation of CO, cardiac index and SV when compared to cardiac magnetic resonance. Therefore, in our study, a method of hemodynamic evaluation capable of reliably recording the changes occurred during IE was used.

Inspiratory muscle weakness, present in about 30 to 50% of patients with HFREF, has been acknowledged as a factor that contributes to exercise limitation, in addition to having an independent prognostic value.[3-5]

One of the main studies with IMT in HF was carried out by Dall'ago et al.,[9] in which 32 patients were randomized into two groups (IMT-placebo and IMT 30%). After 12 weeks of sessions (7 times a week, for 30 minutes), the patients in the intervention group showed a significant increase of 115% in MIP, 17% increase in peak oxygen uptake, and 19% increase in the distance covered in six minutes, in addition to an improvement in quality of life.

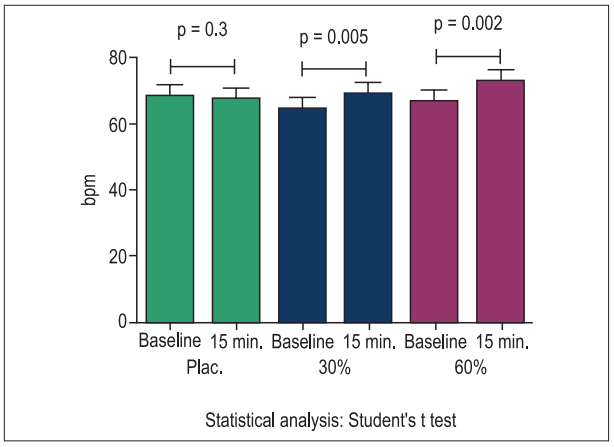


Figure 2 – *HR behavior before and at 15 min. of IE with the different loads. HR: heart rate; IE: inspiratory exercise; bpm: beats per minute; plac: placebo; min: minutes. (Source: The author)*

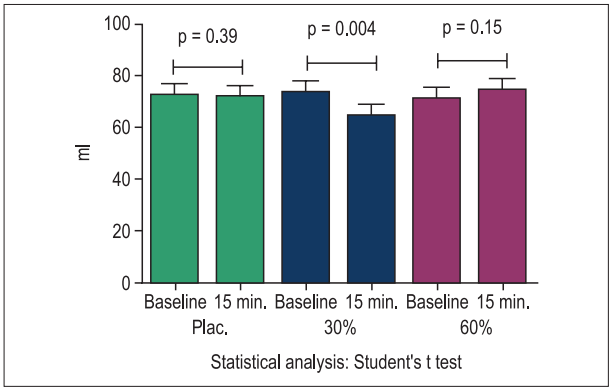


Figure 3 – *Behavior of the SV before and at 15 min. of IE with the different loads. SV: systolic volume; IE: inspiratory exercise; ml: milliliter; plac: placebo; min: minutes. (Source: The author)*

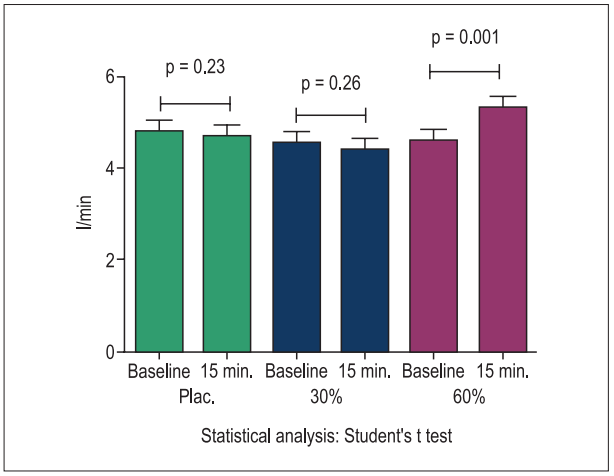


Figure 4 – *Behavior of CO before and at 15 min. of IE with the different loads. CO: cardiac output; IE: inspiratory exercise; ml: milliliter; plac: placebo; min: minutes. (Source: The author)*

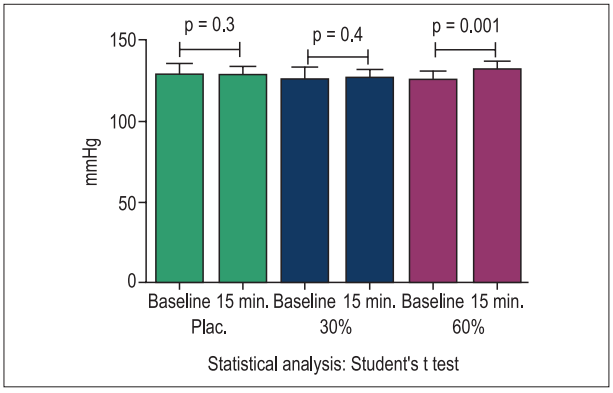


Figure 5 – *SBP behavior in the IE with the different loads. (Baseline 124.1 ± 27.4 vs 15 min. 130.6 ± 25.9 mmHg, p = 0.001). SBP: systolic blood pressure; IE: inspiratory exercise; mmHg: millimeters of mercury; min.: minutes. (Source: The author).*

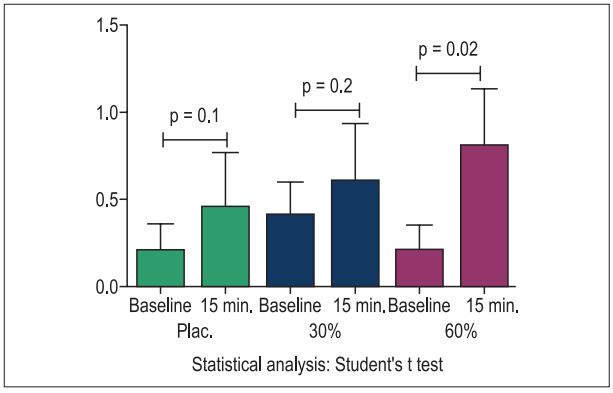


Figure 8 – *Behavior of the subjective scale of dyspnea in IE with different loads. (Baseline 0.2 ± 0.7 vs 15 min. 0.8 ± 1.5, p = 0.02). IE: inspiratory exercise; min.: minutes. (Source: The author)*

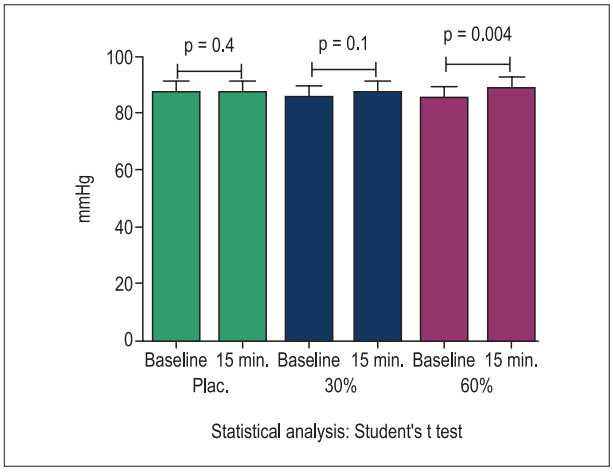


Figure 6 – *MAP behavior in the IE with the different loads. (Baseline 85.7 ± 17.9 vs 15 min. 89.2 ± 17.3 mmHg, p = 0.004). MAP: mean arterial pressure; IE: inspiratory exercise; mmHg: millimeters of mercury; min.: minutes. (Source: The author).*

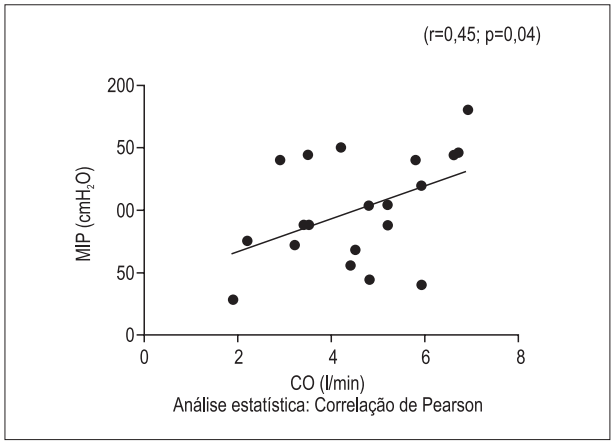


Figure 9 – *Correlation between baseline CO and inspiratory muscle strength, r = 0.45; p = 0.04. CO: cardiac output; l/min: liters per minute; MIP: maximum inspiratory pressure; cm/H_2O: centimeters of water.*

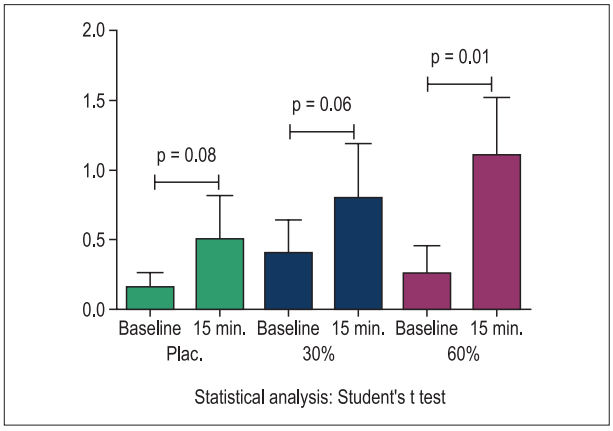


Figure 7 – *Borg results in the IE with different loads. (Basal 0.3 ± 0.9 vs 15 min. 1.1 ± 1.9, p = 0.01). IE: inspiratory exercise; min.: minutes.(Source: The author)*

Studies with inspiratory muscle training, performed since 1995 in HF, have focused on demonstrating the improvement in muscle strength and endurance, improvement in functional capacity and quality of life.[6,7] However, the hemodynamic repercussions of the IE remain unclear.

Hemodynamic variables

When a healthy individual is subjected to a resistive load to exercise, the tendency of the hemodynamic response is to increase SBP, at the same time that the CO will increase and, independently, the components of the formula of this variable. Regarding the intensity of the exercise, there is evidence that the greater the intensity for the same number of repetitions, the greater the increase in HR and blood pressure.[14] In fact, this occurred in the present study because, over the 15 minutes of IE, the highest intensity was responsible for the most significant increases in HR and SBP.

Furthermore, the CO for the different resistive loads increased by 15% with the 60% load and decreased by 3% with the 30% load.

It is known that the increase in CO can occur due to an increase in HR alone, only in SV, or both. In our study, the increase in CO in IE with a 60% load occurred mainly due to the significant increase in HR, with a small participation of SV, since this variable also increased, but on a smaller, non-significant scale. On the other hand, when the 30% load is used, the CO had an inverse behavior and presented a small decrease, even with an increase in HR. In this case, what seems to have been decisive for the non-increase in output was the 12.5% drop in SV.

Some researchers report that, during exercise in patients with HF, a small increase in SV occurs. Others demonstrate that there is no increase in this variable.[14] In this study, the response to a load of 60% was a small increase of 4.5% and a decrease in IE with a 30% load.

The decrease in SV and the increase in HR with a 30% load reported in this study are similar to the hemodynamic repercussions of the Muller maneuver, which also causes negative intrathoracic pressure. Orban et al.[15] studied the hemodynamic effects of the Muller maneuver sustained for 12 seconds in 20 healthy young adults and, among other results, found a decrease in SV and an increase in HR. Hall et al.[16] evaluated the effect of the Muller maneuver sustained for 15 seconds in 8 patients with congestive heart failure and concluded that, during the maneuver, there is an increase in left ventricular afterload and a decrease in systolic volume, but HR did not show significant changes.

However, the pressure required to perform the Muller maneuver is around -40 mmHg (-54 cm/H_2O), and the average load used during IE sessions was -31 cm/H_2O with 30% load and -61 cm/H_2O with 60% load. Thus, the load that came closest to the value for performing the Muller maneuver was not the one with a behavior similar to the maneuver, except for the increase in HR.

McConnell and Griffiths[17] assessed the acute response of HR, BP and MAP to different loads of inspiratory muscle training (50%, 60%, 70%, 80%, and 90%) in 8 athletes. All loads caused an increase in HR, but only a 60% load caused a sustained increase in MAP, SBP and diastolic blood pressure (DBP). In conclusion, the authors suggest an evidence of a response to the activation of the metaborreflex in this load.

The results found by the authors cited above are similar to the findings in this study, where both loads increased HR, but only the load of 60% caused a significant increase in SBP and MAP, which may have occurred due to the activation of the inspiratory metaborreflex.

This hypothesis is in agreement with other studies, in which the authors state that the activation of the inspiratory metaborreflex is manifested by the increase in HR and MAP.[18,19]

The activation of the metaborreflex by inspiratory muscle work is a factor that contributes to exercise intolerance in patients with HF. During the increase in the respiratory work, there is a redistribution of blood flow from the peripheral muscles to the diaphragm, about 14 to 16% of flow theft of CO, causing an exacerbation of fatigue in peripheral muscles.[20]

Corroborating the findings of the present study, Moreno et al.[11] evaluated the effect of respiratory muscle fatigue on oxygenation and perfusion of the intercostal and forearm muscles in patients with HFREF. After inspiratory exercise with a 60% load until fatigue, the authors reported decreased perfusion and oxygenation in both the intercostal muscle and forearm, and suggested that this leads to a reduction in the muscle perfusion reflex of peripheral muscles, activting the inspiratory metaborreflex.

However, in the long run, Chiappa et al.[21] demonstrated that 4 weeks of IMT with a 60% load is able to attenuate the inspiratory metaborreflex in patients with HF and muscle weakness. The authors also reported a significant increase in the Borg score, which did not occur in the control group, whose exercise was performed with only 2% of MIP.

This result is similar to that of our study, where only the highest load significantly increased Borg's score, in addition to raising the score on the subjective dyspnea scale; however, this last scale was not evaluated in the study by Chiappa et al.[21]

High IMT loads (60-70%) are recommended to promote a better effect in patients with HF, while lower loads (20-40%) are indicated for patients with a higher functional class.[3] The present study demonstrated a higher degree of fatigue and dyspnea, as well as greater effects on CHR, during a single session of IE with a 60% load, which corroborates this recommendation and highlights a potential risk for individuals with ischemia and with recent decompensation of HF.

Crisafulli et al.[22] were the first to assess the acute hemodynamic response to the activation of the metaborreflex in humans with HF and to compare it to the response of healthy individuals. For this, nine patients with HFREF and nine healthy volunteers were selected. All were submitted to post-exercise ischemia. The hemodynamic response, as in the present study, was assessed by cardiographic impedance. As a result, the authors reported that the increase in SBP was similar in both groups, but the control group obtained an increase in SBP due to the increase in CO; in the group of patients with HF, this increase occurred due to the increase in systemic vascular resistance (SVR). There was also an increase in SV in the group of healthy individuals and a decrease in this variable in patients with HF. The authors suggest that the increase in SVR occurs due to the inability of patients with HF to improve cardiac performance and SV.

Correlation between CO and MIP

In our study, a moderate correlation between CO and MIP was found.

A similar result was found by Nishimura et al.[23] after evaluating 23 patients with HF. However, the correlation found was between cardiac index and MIP. At that time, the authors already suggested that the inspiratory muscles could be dependent on cardiac function.

More recently, Filusch et al.[24] evaluated 532 patients with congestive heart failure using right heart catheterization and also found a moderate correlation between CO and MIP. The authors state that, as MIP is easily measured in clinical practice, it can become an additional parameter in noninvasive hemodynamic monitoring of disease severity.

Meyer et al.[4] were the first to demonstrate that inspiratory muscle strength has an independent prognostic value. They followed up 244 patients with HFREF for 23 months, and the 57 patients (23%) who died over that period had MIP even more reduced than the rest of the sample.

Corroborating the findings of Meyer, Frankenstein et al.,[5] in a prospective study with 686 patients, showed that MIP can be considered a prognostic value even in patients using β-blockers.

Study limitations

The sample size made it impossible to assess only the group with inspiratory muscle weakness and, given that the present study had an acute effect, we do not know whether these effects are maintained or attenuated. Further investigations are needed to assess chronic IMT-related CHR.

Clinical applicability

These data indicate that the hemodynamic response of the IE in its different proposals of resistive load with the linear load resistor could have a potential for safe applicability in non-drug treatment of patients with HF (NYHA II and III), without adverse effects.

Conclusions

When the 60% load was used in a single session of inspiratory exercise, changes in CHR were observed. Particularly increased heart rate, cardiac output, Borg scale and subjective feeling of dyspnea. The 30% load promoted a decrease in systolic volume. Placebo did not promote significant changes in CHR in the present study and, finally, there was a moderate correlation between cardiac output and inspiratory muscle strength.

Author contributions

Conception and design of the research: Marchese LD, Chermont S, Pereira SB, Mesquita ET; Acquisition of data: Marchese LD, Chermont S, Warol D, Quintão M; Analysis and interpretation of the data: Marchese LD, Chermont S, Warol D, Oliveira LB, Mesquita ET; Statistical analysis: Marchese LD, Chermont S; Writing of the manuscript: Marchese LD, Warol D; Critical revision of the manuscript for intellectual content: Chermont S, Oliveira LB, Pereira SB, Quintão M, Mesquita ET.

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 Luana de Decco Marchese, from Universidade Federal Fluminense.

References

1. Tucker WJ, Haykowsky MJ, Seo Y, Stehling E, Forman DE.Impaired Exercise Tolerance in Heart Failure: Role of Skeletal Muscle Morphology and Function. Curr Heart Fail Rep. 2018. [Epub ahead of print].
2. Achttien RJ, Staal JB, van der Voort S, Kemps HM, Koers H, Jongert MW et al. Exercise-based cardiac rehabilitation in patients with chronic heart failure: a Dutch practice guideline. Neth Heart J. 2015;23(1):6-17.
3. Miyagi M, Kinugasa Y, Sota T, Yamada K, Ishisugi T, Hirai M et al. Diaphragm Muscle Dysfunction in Patients With Heart Failure.J Card Fail. 2018;24(4):209-16.
4. Meyer FJ, Borst MM, Zugck C, Kirschke A, Schellberg D, Kübler W, Respiratory muscle dysfunction in congestive heart failure: clinical correlation and prognostic significance. Circulation. 2001;103(17):2153-8.
5. Frankenstein L, Nelles M, Meyer FJ, Sigg C, Schellberg D, Remppis BA et al. Validity, prognostic value and optimal cutoff of respiratory muscle strength in patients with chronic heart failure changes with beta-blocker treatment. Eur J Cardiovasc Prev Rehabil. 2009;16(4):424-9.
6. Sadek Z, Salami A, Joumaa WH, Awada C, Ahmaidi S, Ramadan W.Best mode of inspiratory muscle training in heart failure patients: a systematic review and meta-analysis. Eur J Prev Cardiol. 2018;25(16):1691-701.
7. Wu J, Kuang L, Fu L. Effects of inspiratory muscle training in chronic heart failure patients: A systematic review and meta-analysis. Congenit Heart Dis. 2018;13(2):194-202.
8. Gomes Neto M, Ferrari F, Helal L, Lopes AA, Carvalho VO, Stein R. The impact of high-intensity inspiratory muscle training on exercise capacity and inspiratory muscle strength in heart failure with reduced ejection fraction: a systematic review and meta-analysis. Clin Rehabil. 2018;32(11):1482-92.
9. Dall'Ago P, Chiappa GR, Guths H, Stein R, Ribeiro JP. Inspiratory muscle training with heart failure and inspiratory muscle weakness. J Am Coll Cardiol. 2006;47(4):757-63.
10. Archiza B, Simões RP, Mendes RG, Fregonezi GA, Catai AM, Borghi-Silva A.Acute effects of different inspiratory resistive loading on heart rate variability in healthy elderly patients.Braz J Phys Ther. 2013;17(4):401-8.
11. Moreno AM, Castro RR, Silva BM, Villacorta H, Sant'Anna Junior M, Nóbrega AC.Intercostal and forearm muscle deoxygenation during respiratory fatigue in patients with heart failure: potential role of a respiratory muscle metaboreflex. Braz J Med Biol Res. 2014;47(11):972-6.
12. Paredes OL, Shite J, Shinke T, Watanabe S, Otake H, Matsumoto D et al. Impedance Cardiography for cardiac output estimation. Circ J. 2006;70(9):1164-8.
13. Villacorta Junior H, Villacorta AS, Amador F, Hadlich M, Albuquerque DC, Azevedo CF Transthoracic impedance compared to magnetic resonance imaging in the assessment of cardiac output. Arq Bras Cardiol. 2012;99(6):1149-55.

14. McConnell TR. A review to develop an effective exercise training for heart failure patients. Eura Medicophys. 2005;41(1):49-56.

15. Orban M, Bruce CJ, Pressman GS, Leinveber P, Romero-Corral A, Korinek J et al. Dynamic changes of left ventricular performance and left atrial volume induced by the mueller maneuver in healthy young adults and implications forobstructive sleep apnea, atrial fibrillation, and heart failure. Am J Cardiol. 2008;102(11):1557-61.

16. Hall MJ, Ando S, Floras JS, Bradley TD. J Magnitude and time course of hemodynamic responses to Mueller maneuvers in patients with congestive heart failure. Appl Physiol. 1998;85(4):1476-84.

17. McConnell AK, Griffiths LA.Acute cardiorespiratory responses to inspiratory pressure threshold loading. Med Sci Sports Exerc. 2010;42(9):1696-703.

18. Witt JD, Guenette JA, Rupert JL, McKenzie DC, Sheel AW. Inspiratory muscle training attenuates the human respiratory muscle metaboreflex.J Physiol. 2007;584(Pt 3):1019-28.

19. St Croix CM, Morgan BJ,Wetter TJ, Dempsey JA. Fatiguing inspiratory muscle work causes reflex sympathetic activation in humans. J Physiol. 2000;529(Pt2):493-504.

20. Harms CA, Wetter TJ, McClaran SR, Pegelow DF, Nickele GA, Nelson WB et al. Effects of respiratory muscle work on cardiac output and its distribution during maximal exercise. J Appl Physiol. 1988;85(2):609-18.

21. Chiappa GR, Roseguini BT, Vieira PJ, Alves CN, Tavares A, Winkelmann ER et al. Inspiratory muscle training improves blood flow to resting and exercising limbs in patients with chronic heart failure. J Am Coll Cardiol. 2008;51(17):1663-71.

22. Crisafulli A, Salis E, Tocco F, Melis F, Milia R, Pittau G et al. Impaired central hemodynamic response and exaggerated vasoconstriction during muscle metaboreflex activation in heart failure patients. Am J Physiol Heart Circ Physiol. 2007;292(6):H2988-96.

23. Nishimura Y, Maeda H, Tanaka K, Nakamura H, Hashimoto Y, Yokoyama M. Respiratory muscle strength and hemodynamics in chronic heart failure. Chest. 1994;105(2):355-9.

24. Filusch A, Ewert R, Altesellmeier M, Zugck C, Hetzer R, Borst MM et al. Respiratory muscle dysfunction in congestive heart failure--the role of pulmonary hypertension.J. Int J Cardiol. 2011;150(2):182-5.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Inspiratory Muscle Training at Different Intensities in Heart Failure: Are There Differences in Central Hemodynamic Changes?

Lucas Helal[1,2,3] *and Filipe Ferrari*[2,4]

Universidade do Extremo Sul Catarinense - UNESC,[1] *Criciúma, SC - Brazil*

Graduate Program in Cardiology and Cardiovascular Sciences, Hospital de Clínicas de Porto Alegre (HCPA), Universidade Federal do Rio Grande do Sul,[2] *Porto Alegre, RS - Brazil*

Centre for Journalology, Ottawa Hospital Research Institute,[3] *Ottawa - Canada*

Exercise Cardiology Research Group (CardioEx), Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul,[4] *Porto Alegre, RS - Brazil*

Short Editorial related to the article: Controlled Study of Central Hemodynamic Changes in Inspiratory Exercise with Different Loads in Heart Failure

Heart failure (HF) is a complex entity and usually has a poor prognosis, identified as an extremely relevant cardiovascular disease due to its increasing incidence, prevalence and high associated morbidity and mortality.[1] It is estimated that its prevalence varies from 1% to 2% in developed countries, reaching >10% in people over 70 years of age; [2] moreover, it is considered the main cause of cardiovascular hospitalization in individuals older than 60 years.[3]

Among the main symptoms characteristic of HF, dyspnea and fatigue stand out, which are closely associated with impaired functional capacity and, consequently, with these individuals' quality of life.[4] Physical training, in turn, has gained a prominent place in recent decades, aiming at improving this scenario, based on increasing evidence; therefore, it has the ability to favorably impact the gain in functional capacity and quality of life of HF patients.[5,6] Among the several types of physical training targeted at this population, inspiratory muscle training (IMT) is known for being easy to apply and showing potential benefits in this scenario.

Inspiratory muscle training in heart failure

There is robust evidence suggesting that the weakness of inspiratory muscles is one of the main factors that lead to low exercise tolerance in patients with HF.[7,8] In fact, randomized clinical trials have shown several benefits of IMT in patients with this syndrome, namely: significant improvement in oxygen uptake efficiency,[9] functional capacity and quality of life scores.[10] These results were confirmed by meta-analyses, such as that carried out by Smart et al.[11] When compared to the control group, patients undergoing IMT achieved an important improvement in maximum oxygen consumption (VO_2max): 1.83 mL.kg^{-1}.min^{-1} (95%CI, 1.33 for 2.32 mL.kg^{-1}.min^{-1}, p <0.00001), as well as in the 6-minute walking test: 34.35 m (95%CI, 22.45 to 46.24 m, p <0.00001). In turn, inspiratory muscle strength seems to have a significant correlation with VO_2max, which is an independent predictor of survival in individuals with HF.[12] IMT should therefore be an integral part of these patients' care whenever possible.

In this issue of the *Arquivos Brasileiros de Cardiologia*, a randomized, placebo-controlled trial[13] evaluated the implications of an acute session of different intensities of IMT on the central hemodynamic response (CHR) of individuals with HF, using a non-invasive monitoring method. For this purpose, 20 patients with reduced ejection fraction (37.2% ± 6.3%), a mean age of 65 years, and the vast majority in New York Heart Association (NYHA) functional class II were included in the study. The IMT protocol consisted of 3 sessions lasting 15 minutes each. All participants underwent the training with an intensity of 30% and 60% of maximum inspiratory pressure (MIP), in addition to sham intervention (placebo), with a 1-hour washout between them. It was observed that CHR behaved in a heterogeneous way between intensities. For instance, there was an increase in heart rate with intensities of 30% and 60% of MIP (64 ± 15 to 69 ± 15 beats per minute; and 67 ± 14 to 73 ± 14 beats per minute, respectively). Regarding stroke volume, there was a tendency to decrease with a 30% load of MIP (73 ± 26 mL to 64 ± 20 mL). The cardiac output increased only in the group with the highest intensity (4.6 ± 1.5 L / min to 5.3 ± 1.7 L / min), a behavior that was similar in relation to the systolic blood pressure response. In fact, the increase in cardiac output observed at the highest applied intensity can be partially explained by the increase in heart rate in this group. These findings should not be ignored, since patients with HF tend to have impaired blood flow to the active muscles, secondary to reductions in cardiac output and peripheral vasodilator capacity. These changes are harmful, causing important intolerance to effort, being associated with reduced vasodilator capacity and increased sympathetic stimulation, common in these individuals.[14]

Recently, in a systematic review with meta-analysis, our group showed that high-intensity IMT (≥ 60% of MIP) can be an efficient strategy to improve functional capacity and inspiratory muscle strength in this same class of patients

Keywords

Heart Failure; Maximal Respiratory Pressures; Heart Rate; Stroke Volume; Cardiac Output; Hemodynamic Monitoring/methods.

Mailing Address: Lucas Helal •
Universidade do Extremo Sul Catarinense - UNESC, Criciúma, Santa Catarina, Brazil, 88806-000
E-mail: lh@unesc.net

DOI: https://doi.org/10.36660/abc.20200162

(that is: HF and reduced ejection fraction).[15] In turn, we believe that the referred study[13] adds important knowledge to the literature, showing differences in the hemodynamic repercussions observed in the IMT at different intensities, an area little explored so far. These findings may open new horizons and perspectives, influencing further research exploring the hemodynamic responses of IMT in patients with HF. The lack of a close correlation between central hemodynamics (such as the sympathetic nervous system hyperactivation) and exercise tolerance strengthens the importance of the results of this study.

References

1. Ziaeian B, Fonarow GC. Epidemiology and aetiology of heart failure. Nat Rev Cardiol. 2016;13(6):368-78.
2. Choi HM, Park MS, Youn JC. Update on heart failure management and future directions. Korean J Intern Med. 2019;34(1):11-43.
3. Rossignol P, Hernandez AF, Solomon SD, Zannad F. Heart failure drug treatment. Lancet. 2019;393(10175):1034-44.
4. Daher A, Matthes M, Keszei A, Brandenburg V, Müller T, Cornelissen C, et al. Characterization and Triggers of Dyspnea in Patients with Chronic Obstructive Pulmonary Disease or Chronic Heart Failure: Effects of Weather and Environment. Lung. 2019;197(1):21-8.
5. Alvarez P, Hannawi B, Guha A. Exercise And Heart Failure: Advancing Knowledge And Improving Care. Methodist Debakey Cardiovasc J. 2016;12(2):110-5.
6. Cattadori G, Segurini C, Picozzi A, Padeletti L, Anzà C. Exercise and heart failure: an update. ESC Heart Fail. 2018;5(2):222-32.
7. McParland C, Resch EF, Krishnan B, Wang Y, Cujec B, Gallagher CG. Inspiratory muscle weakness in chronic heart failure: role of nutrition and electrolyte status and systemic myopathy. Am J Respir Crit Care Med. 1995;151(4):1101-7.
8. Verissimo P, Casalaspo TJ, Gonçalves LH, Yang AS, Eid RC, Timenetsky KT. High prevalence of respiratory muscle weakness in hospitalized acute heart failure elderly patients. PLoS One. 2015;10(2):e0118218.
9. Stein R, Chiappa GR, Güths H, Dall'Ago P, Ribeiro JP. Inspiratory muscle training improves oxygen uptake efficiency slope in patients with chronic heart failure. J Cardiopulm Rehabil Prev. 2009;29(6):392-5.
10. Dall'Ago P, Chiappa GR, Guths H, Stein R, Ribeiro JP. Inspiratory muscle training in patients with heart failure and inspiratory muscle weakness: a randomized trial. J Am Coll Cardiol. 2006;47(4):757-63.
11. Smart NA, Giallauria F, Dieberg G. Efficacy of inspiratory muscle training in chronic heart failure patients: a systematic review and meta-analysis. Int J Cardiol. 2013;167(4):1502-7.
12. Cahalin LP, Arena R, Guazzi M, Myers J, Cipriano G, Chiappa G, et al. Inspiratory muscle training in heart disease and heart failure: a review of the literature with a focus on method of training and outcomes. Expert Rev Cardiovasc Ther. 2013;11(2):161-77.
13. Marchese LD, Chermont S, Warol D, Oliveira LB, Pereira SB, Quintão M, et al.Controlled Study of Central Hemodynamic Changes in Inspiratory Exercise with Different Loads in Heart Failure. Arq Bras Cardiol. 2020; 114(4):656-663.
14. Piña IL, Apstein CS, Balady GJ, Belardinelli R, Chaitman BR, Duscha BD, et al. Exercise and heart failure: A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. Circulation. 2003;107(8):1210-25.
15. Gomes Neto M, Ferrari F, Helal L, Lopes AA, Carvalho VO, Stein R. The impact of high-intensity inspiratory muscle training on exercise capacity and inspiratory muscle strength in heart failure with reduced ejection fraction: a systematic review and meta-analysis. Clin Rehabil. 2018;32(11):1482-92.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Prognostic Value of NT-proBNP versus Killip Classification in Patients with Acute Coronary Syndromes

Thiago M. B. Souza,[1] Antônio Maurício S. Cerqueira Jr.,[1] Jessica G. Suerdieck,[1] Nicole C. de Sá,[1] Gabriella S. Sodré,[1] Vitor C. A. Correia,[1] Yasmin F. Lacerda,[1] Leticia L. Fonseca,[1] Marcia M. Noya-Rabelo,[2] Luis C. L. Correia[1]

Escola Bahiana de Medicina e Saúde Pública,[1] Salvador, BA – Brazil

Hospital São Rafael,[2] Salvador, BA – Brazil

Abstract

Background: Plasma levels of brain natriuretic peptides have better diagnostic accuracy compared to clinical-radiologic judgment for acute heart failure. In acute coronary syndromes (ACS), the prognostic value of acute heart failure is incorporated into predictive models through Killip classification. It is not established whether NT-proBNP could increment prognostic prediction.

Objective: To evaluate whether NT-proBNP, as a measure of left ventricular dysfunction, improves the in-hospital prognostic value of the GRACE score in ACS.

Methods: Patients admitted due to acute chest pain, with electrocardiogram and/or troponin criteria for ACS were included in the study. The plasma level of NT-proBNP was measured at hospital admission and the primary endpoint was defined as cardiovascular death during hospitalization. P-value < 0.05 was considered as significant.

Results: Among 352 patients studied, cardiovascular mortality was 4.8%. The predictive value of NT-proBNP for cardiovascular death was shown by a C-statistic of 0.78 (95% CI = 0.65–0.90). After adjustment for the GRACE model subtracted by Killip variable, NT-proBNP remained independently associated with cardiovascular death (p = 0.015). However, discrimination by the GRACE-BNP logistic model (C-statistics = 0.83; 95%CI = 0.69–0.97) was not superior to the traditional GRACE Score with Killip (C-statistic = 0.82; 95%CI = 0.68–0.97). The GRACE-BNP model did not provide improvement in the classification of patients to high risk by the GRACE Score (net reclassification index = – 0.15; p = 0.14).

Conclusion: Despite the statistical association with cardiovascular death, there was no evidence that NT-proBNP increments the prognostic value of GRACE score in ACS. (Arq Bras Cardiol. 2020; 114(4):666-672)

Keywords: Acute Coronary Syndrome; Heart Failure; Natriuretic Peptide, Brain; Mortality; Ventricular Dysfunction, Left; Biomarkers.

Introduction

Brain natriuretic peptide is a prohormone, biologically measured by its active fragment or its inactive terminal portion (NT-proBNP). These molecules are biomarkers of left ventricular dysfunction, released to the bloodstream by myocytes undergoing wall tension due to volumetric or pressure overload.[1] In the detection of heart failure, these peptides present better accuracy than clinical-radiological evaluation, being able to identify sub-clinical levels of decompensation.[2]

The presence of left ventricular dysfunction is an important determinant of prognosis in patients with acute coronary syndromes (ACS). In this context, multivariate predictive models[3,4] take into account the presence of clinically manifested left ventricular dysfunction, well represented by the classification of Killip and Kimball.[5] Two reasons support the hypothesis that the use of plasma biomarkers may increase the prognostic value of these models: the capacity to numerically quantify the degree of cardiac decompensation and the higher sensitivity for subclinical changes, without impairing specificity.[2]

In the context of ACS, the concentration of NT-proBNP has a well-documented prognostic accuracy.[6] However, from a predictive point of view, whether NT-proBNP has an incremental value in relation to probabilistic models that already contain Killip as a predictor variable is a controversial matter.[7-9] Among the models validated for risk prediction, GRACE score is the one with the best prognostic accuracy, containing Killip class as the marker of heart failure.[10-12] In this cohort, we tested the hypothesis that NT-proBNP incorporation increases the prognostic value of the GRACE score in patients with ACS. NT-proBNP was measured at admission and the primary outcome was defined as cardiovascular death during hospitalization.

Mailing Address: Luis Correia •
Escola Bahiana de Medicina e Saúde Pública – Av. Princesa Leopoldina, 19/402. Postal Code 40050-420, Salvador, BA – Brazil
E-mail: lccorreia@cardiol.br
Manuscript received November 13, 2018, revised manuscript May 20, 2019, accepted June 05, 2019

DOI: https://doi.org/10.36660/abc.20180345

Methods

Sample selection

Patients consecutively admitted to the coronary care unit (CCU) of a tertiary-care hospital, between September 2007 and October 2013, due to suspected ACS (unstable angina and myocardial infarction) were prospectively included in the study. Inclusion criteria was chest discomfort in addition to at least one of the three objective criteria:

1) positive biological marker of myocardial necrosis, defined as troponin T ≥ 0.01 ug/L or troponin I > 0.034 g/L, corresponding to values above the 99th percentile;[13]
2) ischemic electrocardiographic alteration, consisting of T wave inversion (≥ 0.1 mV) or ST segment changes (≥ 0.05 mV); and
3) previously documented coronary artery disease, defined as a history of myocardial infarction with Q wave or previous angiography demonstrating coronary obstruction ≥ 70%.

Patients without NT-proBNP dosage or who did not agree to participate in the study were excluded. The protocol was in compliance with the Declaration of Helsinki, was approved by the Research Ethics Committee of the Institution, and all participants provided written informed consent.

NT-proBNP Measurement

NT-proBNP measurement was performed on a blood sample collected at patient's arrival at the hospital, aiming for a minimum delay between the onset of symptoms and the collection of material. Plasma was frozen at –70 °C for simultaneous dosing of the samples. The immunoassay method (Biomérieux) was used, considering the following definitions of high NT-proBNP:

1) Values above 450 pg/ml in patients under 50 years of age;
2) Values above 900 pg/ml in patients over 50 years of age.[2]

GRACE score

The GRACE score calculation was based on clinical data at admission, electrocardiogram performed within 6 hours of admission, troponin T or troponin I dosages in the first 12 hours, and the first plasmatic creatinine. Elevation of myocardial necrosis markers (as a component of the scores) was defined as troponin above the 99th percentile. The GRACE score includes eight variables: five semi-quantitative, meaning different weight for each age stratum (systolic blood pressure, heart rate, plasma creatinine and Killip class), and three dichotomic ones (ST segment depression, elevation of myocardial necrosis marker, and cardiac arrest at admission). The final score can range from 0 to 372.[3]

Clinical end-point

The clinical end-point was cardiovascular death during hospitalization, defined by one of the following mechanisms: cardiac failure, arrhythmia or due to complications from treatments related to ACS.

Statistical Analyses

Numerical variables were expressed as mean and standard deviation as they presented normal distribution or small deviation from normality, while median and interquartile range were preferred in case of significant deviation from normality. Categorical variables were expressed in proportions. Preliminary results were accompanied by a 95% confidence interval as a measure of uncertainty. Initially, predictive values of NT-proBNP and Killip class were evaluated by the area under the ROC curve (C-statistic), considering cardiovascular death as an outcome. These two curves were statistically compared by the Hanley-McNeil paired test.[14] In addition, Kappa Test was used to assess concordance between high NT-proBNP and Killip > I in the definition of heart failure.

Logistic regression was used to assess the incremental value of NT-proBNP to the GRACE Score. The technique of modifying the GRACE Score was used, by replacing Killip for NT-proBNP, and then comparing this GRACE-BNP model to the traditional GRACE. The modification of GRACE was performed in two ways, one numerical and another categorical. In the first case, the regression coefficient of NT-proBNP represented the change in log odds promoted by each unit of NT-proBNP. In this case, the logistic regression equation determined the weight of NT-proBNP (numerical GRACE-BNP). In the second case, a high NT-proBNP added 20 points to the Killip free GRACE, which is the equivalent of Killip II value in the score (categorical GRACE-BNP).

The C-statistics of both models were compared with the traditional GRACE Score by the Hanley-McNeil test. Finally, net reclassification index analysis by Pencina[15] was used to evaluate the reclassification value of logistic and categorical GRACE-BNP in relation to the definition of high risk. For this reclassification, the best cutoff points for these new scores were used in the ROC curve.

Regarding sample size definition, two criteria were used. Firstly, aiming to reach a power of 80% to detect a difference of 0.05 between two ROC curves (referring to scores) and predicting a correlation of 0.80 between the scores, it would be necessary to enroll 192 patients. Secondly, in order to insert two variables in a logistic regression model, 10 to 20 events would be necessary.[16]

All of the tests above were considered statistically significant if p-value < 0.05. The SPSS Version 21 was the software used for the analysis.

Results

Sample characteristics

The sample consisted of 352 patients, mean age 63 ± 14 years, 60% male, 26% presenting with ST-segment elevation myocardial infarction. The GRACE score had a median of 104 (IIQ 82 - 131), which corresponds to intermediate risk. The median of NT-proBNP was 340 pg/ml (IIQ 86-1212), elevated in 29% of patients. The median time between symptom onset and NT-pro-BNP dosage was 15.5 hours (IIQ 8.2 - 32.5). The incidence of cardiovascular death in the hospital phase was 4.8%. Sample characteristics are described in Table 1.

Table 1 – Clinical and laboratorial characteristics of the selected sample

Variable	N
Sample Size	352
Age (years)	63 ± 14
Male Gender	210 (60%)
ACS	
Unstable angina	102 (29%)
NSTEMI	90 (26%)
STEMI	160 (45%)
Triarterial disease or LMCA	170 (48%)
Ischemic ECG	223 (63%)
Positive Troponin	250 (71%)
Creatinine	1.0 ± 0.62
Killip Classification	
Killip I	308 (88%)
Killip II	18 (5%)
Killip III	25 (7%)
Killip IV	1 (0.3%)
NT-proBNP (pg/ml)	340 (86 – 1212)
GRACE score	104 (82 – 131)
Mortality	17 (4.8%)

**ACS: acute coronary syndrome; NSTEMI: Non ST elevation myocardial infarction; STEMI: ST elevation myocardial infarction; LMCA: left main coronary artery; ECG: electrocardiogram; BNP: brain natriuretic peptide.*

NT-proBNP and Killip: Univariate Predictor Value

NT-proBNP demonstrated a moderate predictive capacity for cardiovascular death, according to C-statistic of 0.78 (95% CI = 0.65-0.90, p < 0.001), while the Killip score presented C-statistic of 0.69 (95% CI = 0.54-0.84, p = 0.008), with no statistical difference between the two curves (p = 0.29) (Figure 1). The two markers agreed in the definition of heart failure in 75% of the cases (8% with heart failure and 67% without hear failure), meaning low level of agreement according to the Kappa test (κ = 0.26; 95% CI = 0.54-0.84; p < 0.001).

Independent and Incremental NT-pro-BNP Value

In the logistic regression analysis, numerical NT-proBNP did not maintain statistical significance after adjustment for the traditional GRACE score (p = 0.11). On the other hand, numerical NT-proBNP remained an independent predictor when adjusted for GRACE score without Killip (p = 0.015; for each 500 pg/ml increase in NT-proBNP, a Beta of 0.029 was observed, OR = 1.03; 95% CI = 1.006 - 1.05) (Table 2). Categorical NT-proBNP was not an independent predictor after adjustment for the GRACE score (p = 0.91) or for the GRACE score without Killip (p = 0.36).

For analysis of the incremental value of NT-proBNP to GRACE, we compared the C-statistics of the logistic GRACE-BNP, categorical GRACE-BNP and traditional GRACE score. The results of the analysis were, respectively, 0.83 (95% CI = 0.69-0.97), 0.82 (95% CI = 0.68-0.96), and 0.82 (95% CI = 0.68-0.97). Therefore, no incremental value of the new approaches was identified (Figure 2).

Reclassification of GRACE Score by NT-pro-BNP

Regarding the net reclassification analysis, of the 17 patients who died, 3 were correctly reclassified by logistic GRACE-BNP from low to high risk, with no incorrect reclassification, resulting in a positive net reclassification index (+ 0.18%). Among the 335 patients who survived, 9 were erroneously reclassified from low to high risk, while there was no correct reclassification. This resulted in a negative net reclassification ratio (-0.02%). In the final analysis, considering all patients, the total net reclassification index (NRI) was - 0.15% (p = 0.14) (Table 03). Reclassification based on categorical GRACE-BNP showed similar results (NRI = 0.08; p = 0.44). (Table 3)

Discussion

The present study demonstrates the independent prognostic value of numeric NT-proBNP after adjustment to the GRACE score. However, the NT-proBNP did not improve discrimination of the GRACE Score, nor its reclassification ability. Its findings are in line with the notions that not every independent predictor offers incremental value to traditional models.[17]

In an explanatory point of view, our findings reinforce that the status of cardiac decompensation increases the risk of patients with ACS. On the other hand, from the predictive point of view, refining the prognostic evaluation with a biomarker of heart failure that is more accurate than clinical evaluation was not enough to increase the accuracy of multivariate models. This discussion is intended to debate the potential explanations for the absence of an incremental value, to confront this paper's results with external evidence, to recognize methodological limitations and to address the relevance of the present results.

Different hypotheses may explain the absence of NT-proBNP incremental value. Three possibilities will be pointed out, which comprises the generic properties of predictors and the specificities of the clinical context in question. First, probabilistic models are created with variables that simultaneously contribute to risk prediction, each with a predictive weight that is proportional to its independent strength of association. The improvement of a single predictor (detection of ventricular dysfunction) among many may not represent a relevant change. In the present case, the incorporation of a marker related to a new phenomenon was not proposed, but rather only the replacement of the evaluation of the phenomenon of heart failure with a theoretically better marker. Second, the predictive capacity of NT-proBNP theoretically lies in its continuous characteristic (numerical variable) and in its ability to identify subclinical ventricular dysfunction. It is possible that the prognostic value of heart failure is not at initial levels, limiting to more advanced and clinically manifested degrees. Finally, the prognostic accuracy of the traditional GRACE Score is already satisfactory, represented by C-statistic above 0.8, making more difficult to improve a marker that functions with good predictive capacity.

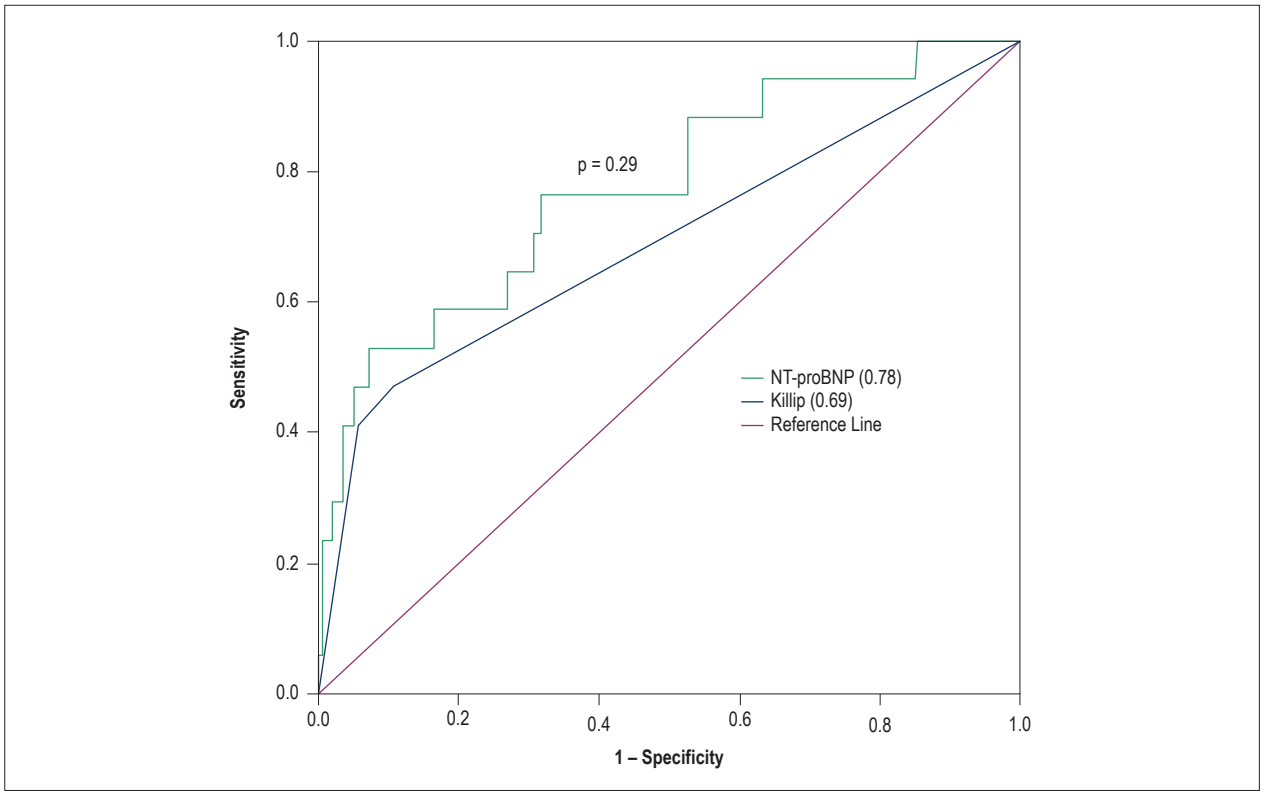


Figure 1 – *The accuracy of NT-pro-BNP in the prediction of death has a value of 0.78 (95% CI 0.65 – 0.9) in the C statistic and in the Killip classification 0.69 (95% CI 0.54 – 0.84).*

Table 2 – Logistic regression model containing GRACE without Killip and numerical NT-proBNP in predicting deaths

Variables	Beta Coefficient	Odds ratio (95% IC)	p Value
GRACE without Killip	0.043	1.04 (1.02 – 1.06)	<0.001
NT-proBNP / 500 pg/ml	0.000	1.03 (1.006 – 1.05)	0.015

Some previous studies have tested the prognostic value of brain natriuretic peptides in ACS. Although there is a disagreement between studies, a careful analysis of the results shows that they all point in the same direction. Three studies conclude positively regarding the prognostic value of this type of marker; however, these studies evaluated the independent predictive value but did not test incremental value (discrimination or reclassification).[18-22] In this context, our results are not discordant. However, our negative conclusion resides in a more comprehensive analysis that was not previously done. In concordance, the two studies that evaluated the incremental value of multivariate models presented the same conclusion as ours.[7,8]

Two aspects are original in the present work: it was the first study to aggregate the analysis of reclassification proposed by Pencina and the only one to adjust for the GRACE score after removal of Killip, avoiding eventual collinearity between Killip and NT-proBNP which could induce type II error. These approaches bring more veracity to our negative outcome.

Methodological limitations must be recognized here, which may have promoted a false negative result. Firstly, it is known that, ideally, a risk marker should be tested in an environment where the care team is not aware of its outcome. As this marker is already available in our clinical practice, the team became aware of the NT-proBNP result, predisposing to performance bias, which could improve the prognosis of patients with high NT-proBNP. Secondly, although this study had the planned sample size, it lacked additional power for exploratory analyses. For example, it was not possible to test the incremental value of the best NT-proBNP cutoff point. To do so, it would require a sample to identify the best cutoff point and another one to test for its incremental value. However, given our sample size, we chose not to split the sample.

The value of a negative result should be contextualized. Frequently, improper evaluation of markers modifies clinical reasoning with no probabilistic basis. That is, after estimating the risk based on the GRACE score, our evaluation would become less accurate if we mentally increased the risk after observing a high NT-proBNP value. It would be an improper reclassification. Therefore, it must be considered that the GRACE score has better accuracy than NT-proBNP, which should not modify the message of the first. On the other hand, the absence of prognostic value should not discredit the value of BNP in diagnosing symptoms of dyspnea during hospitalization or in monitoring the volemic status of patients who developed acute heart failure.

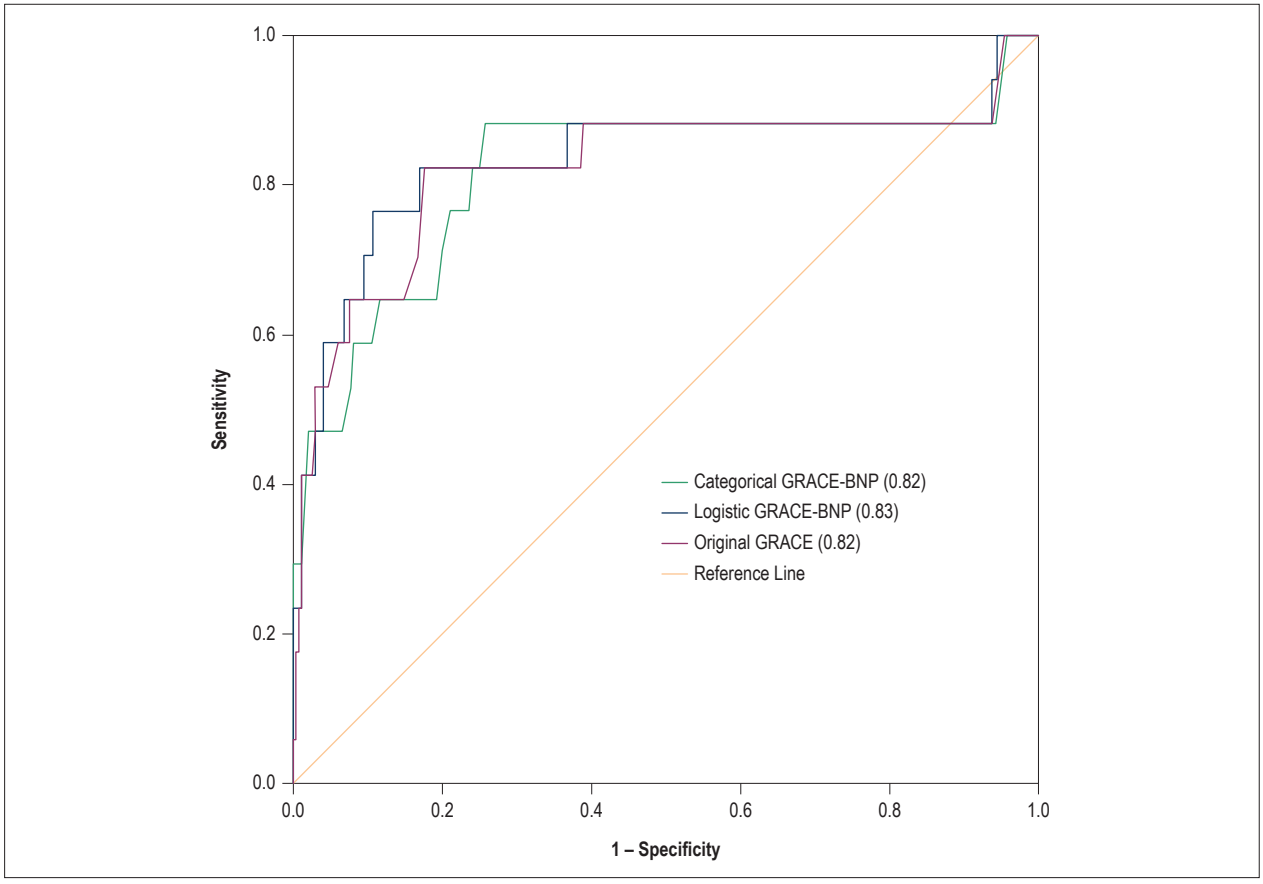


Figure 2 – *Comparison of the ROC curves between original GRACE (0.82; 95% CI = 0.68-0.97) and GRACE-BNP logistic (0.83; 95% CI = 0.69-0.97) and categorical (0.82; 95% CI = 0.68-0.96) shows similar C-statistics among the three scores.*

Table 3 – Analysis of net reclassification by the GRACE-BNP numerical score in relation to the GRACE score in the definition of high risk

	N	Reclassification to high risk	Reclassification to low risk	NRI	p Value
Outcome	17	3	0	+0.18%	
Without outcome	335	9	0	-0.02%	
Total	352	12	0	-0.15%	0.14

Conclusion

Despite its association with risk in a univariate approach, it has not been proven that the use of NT-proBNP as a measure of left ventricular dysfunction increases the in-hospital prognostic value of GRACE score in ACS.

Author contributions

Conception and design of the research: Souza TMB, Cerqueira Jr. AMS, Correia L; Acquisition of data: Souza TMB, Cerqueira Jr. AMS, Suerdieck JG, Sá NC, Sodré GS, Correia VCA, Lacerda YF, Fonseca LL, Noya-Rabelo MM; Analysis and interpretation of the data: Souza TMB, Cerqueira Jr. AMS, Suerdieck JG, Sá NC, Sodré GS; Statistical analysis: Souza TMB, Cerqueira Jr. AMS, Suerdieck JG, Sá NC, Correia VCA, Lacerda YF, Fonseca LL, Noya-Rabelo MM, Correia L; Critical revision of the manuscript for intellectual content: Souza TMB, Cerqueira Jr. AMS, Suerdieck JG, Sá NC, Sodré GS, Correia VCA, Lacerda YF, Fonseca LL, Noya-Rabelo MM, Correia L.

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 Monte Tabor under the protocol number 36/11. 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.

References

1. Hall C. Nt-probnp: the mechanism behind the marker. J Card Fail. 2005;11(5 suppl):S81-3.
2. Januzzi JL Jr, Camargo CA, Anwaruddin S, Baggish AL, Chen AA, Krauser DG, et al. The n-terminal pro-bnp investigation of dyspnea in the emergency department (pride) study. Am J Cardiol. 2005;95(8):948-54.
3. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med. 2003;163(19):2345-53.
4. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, et al. TIMI risk score for st-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous npa for treatment of infarcting myocardium early ii trial substudy. Circulation. 2000;102(17):2031-7.
5. Killip T 3rd, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. Am J Cardiol. 1967;20(4):457-4.
6. Zeng X, Li L, Su Q. The prognostic value of n-terminal pro-brain natriuretic peptide in non-st elevation acute coronary syndromes: a meta-analysis. Clin Chem Lab Med. 2012;50(4):731-9.
7. Meune C, Drexler B, Haaf P, Reichlin T, Reiter M, Meissner J, et al. The grace score's performance in predicting in-hospital and 1-year outcome in the era of high-sensitivity cardiac troponin assays and b-type natriuretic peptide. Heart. 2011;97(18):1479-83.
8. Timoteo AT, Toste A, Ramos R, Miranda F, Ferreira ML, Oliveira JA, et al. Does admission nt-probnp increase the prognostic accuracy of grace risk score in the prediction of short-term mortality after acute coronary syndromes? Acute Card Care. 2009;11(4):236-42.
9. Guidez T, Marechaux S, Pincon C, Lamour H, Barrailler S, Decourcelle V, et al. Addition of b-type natriuretic peptide to the grace score to predict outcome in acute coronary syndrome: A retrospective (development) and prospective (validation) cohort-based study. Emerg Med J. 2012;29(4):274-9.
10. Goncalves PA, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTE-ACS. Eur Heart J. 2005;26(9):865-72.
11. Yan AT, Yan RT, Tan M, Casanova A, Labinaz M, Sridhar K, et al. Risk scores for risk stratification in acute coronary syndromes: useful but simpler is not necessarily better. Eur Heart J. 2007;28(9):1072-8.
12. Correia LC, Freitas R, Bittencourt AP, Souza AC, Almeida MC, Leal J, et al. Prognostic value of grace scores versus timi score in acute coronary syndromes. Arq Bras Cardiol. 2010;94(5):613-9.
13. Apple FS, Quist HE, Doyle PJ, Otto AP, Murakami MM. Plasma 99th percentile reference limits for cardiac troponin and creatine kinase mb mass for use with European Society of Cardiology/American College Of Cardiology consensus recommendations. Clin Chem. 2003;49(8):1331-6.
14. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology. 1983;148(3):839-43.
15. Xanthakis V, Sullivan LM, Vasan RS, Benjamin EJ, Massaro JM, D'Agostino RB, et al. Assessing the incremental predictive performance of novel biomarkers over standard predictors. Stat Med. 2014;33(15):2577-84.
16. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996;49(12):1373-9.
17. Yeboah J, McClelland RL, Polonsky TS, Burke GL, Sibley CT, O'Leary D, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA. 2012;308(8):788-95.
18. Almeida R, Mariano L, Gavina C, Pinho T, Vasconcelos M, Ferreira A, et al. The value of nt-probnp in early risk stratification of acute coronary syndromes. Rev Port Cardiol. 2006;25(1):71-5.
19. Bassan F, Bassan R, Esporcatte R, Santos B, Tura B. Very long-term prognostic role of admission bnp in non-st segment elevation acute coronary syndrome. Arq Bras Cardiol. 2016;106(3):218-25.
20. Galvani M, Ottani F, Oltrona L, Ardissino D, Gensini GF, Maggioni AP, et al. N-terminal pro-brain natriuretic peptide on admission has prognostic value across the whole spectrum of acute coronary syndromes. Circulation. 2004;110(2):128-34.
21. Ranjith N, Pegoraro RJ, Naidoo DP, Esterhuizen TM. Prognostic value of n-terminal-pro-brain natriuretic peptide measurements in patients with acute coronary syndromes. Cardiovasc J S Afr. 2006;17(2):60-6.
22. Vieira C, Nabais S, Ramos V, Braga C, Gaspar A, Azevedo P, et al. Multimarker approach with cystatin c, n-terminal pro-brain natriuretic peptide, c-reactive protein and red blood cell distribution width in risk stratification of patients with acute coronary syndromes. Rev Port Cardiol. 2014;33(3):127-36.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Is Grace Risk Score the Holy Grail in Risk Stratification or Can We Improve it Even Further with Additional Biomarkers?

Ana Teresa Timóteo

Serviço de Cardiologia - Hospital Santa Marta - Centro Hospitalar Universitário Lisboa Central, Lisboa – Portugal

Short Editorial related to the article: Prognostic Value of NT-proBNP versus Killip Classification in Patients with Acute Coronary Syndromes

B-type natriuretic peptide (BNP) has been recognized as a very useful marker for the detection of acute and chronic left ventricular dysfunction, both systolic and diastolic, that can be present in the context of sudden and prolonged myocardial ischemia.[1,2] These are the first steps in the ischemic cascade, leading to cell necrosis. For that reason, natriuretic peptides are usually elevated in the context of acute coronary syndromes.[2]

Myocardial ischemia, even in the absence of left ventricular dysfunction, augments cardiac BNP gene expression, increasing plasma NT-proBNP concentrations.[3,4] BNP kinetics usually peaks at 16 hours of symptom's onset in ST-elevation myocardial infarction and a second peak is usually observed by the fifth day.[5] We can speculate that the first peak might be associated with ischemia and the second peak to left ventricular dysfunction associated with cell necrosis and early remodelling.

N-terminal-pro-BNP (NT-proBNP) is the amino-terminal product after cleavage of the precursor peptide of BNP. It has a longer half-life, allowing greater accumulation and sensitivity in detecting subtle structural and functional changes.[5,6] NT-proBNP has been extensively studied in the last two decades, particularly in the 00's, and results consistently showed that early measurements provide important and independent information for risk stratification across the entire spectrum of acute coronary syndromes.[7-10] Prognostic accuracy of early NT-proBNP measurements is even better when compared to early cardiac troponin measurements, reflecting the ischemic insult rather than cell necrosis.[9]

GRACE risk score is currently the most widely recommended risk stratification score in the context of acute coronary syndromes.[11,12] It incorporates clinical, electrocardiogram and biochemical markers and it is highly predictive for short- and medium-term mortality. For in-hospital mortality, values of Area Under Curve > 0.85 are usually obtained.[7] However, previous studies did not show any additional benefit with the inclusion of natriuretic peptides in this risk stratification tool.[7]

The article by Souza et al.[13] studied the independent predictive value of NT-pro-BNP compared to Killip-Kimbal class in patients with the whole spectrum of acute coronary syndromes and the potential incremental value when included in GRACE risk score in substitution of Killip class.[13] They studied 352 patients with a mean age of 63 years, 60% males, 26% with ST-elevation myocardial infarction and in-hospital cardiovascular mortality was 4.8%. NT-pro-BNP was measured on admission, at a median of 15.5 hours after symptoms onset and 29% showed increased levels. NT-pro-BNP showed a moderate predictive accuracy with an AUC of 0.78, better than Killip class. However, it was not superior compared to the traditional GRACE risk score (AUC 0.82) or when included in GRACE score (AUC 0.83). There was also no benefit in terms of reclassification analysis.

The results presented are in line with previous studies, confirming, in a contemporaneous cohort of patients, the independent prognostic value of admission NT-proBNP in acute coronary syndromes and AUC results were also similar. The main originality of the present paper is the use of this biomarker not as an add-on but in substitution for Killip class, one of the clinical markers of GRACE risk score, justified by the collinearity expected between Killip class and NT-proBNP. However, even with this approach, NT-proBNP didn't improve the prognostic accuracy of the GRACE risk score. I believe that the main explanation is that GRACE risk score is such a potent score, with an AUC usually reported as > 0.85, including already very important prognostic variables, that is very difficult to improve even further this prognostic accuracy. Several other markers were tested by other authors and similar results of no significant improvements were obtained. Could the results be different in long-term follow-up? This is an important question that can be answered in subsequent studies.

There are also some additional limitations to the present study. Inclusion was performed for six years, but only 352 patients were included. Albeit the sample is adequate according to the sample size study presented, it suggests that the inclusion was not consecutive, and several patients were not considered. This is a potential source of bias. Another important fact is that no data is presented about important baseline characteristics. For that reason, we cannot assess if the sample really represents the usual patient's characteristics in acute coronary syndromes cohorts. We also do not know what were the adjustments made in multivariate analysis. That is if all variables with a possible impact in prognosis and in NT-proBNP levels were considered in the multivariate adjustment. The "heart failure" definition used by the authors is also not clearly explained.

In conclusion, the present study shows that in a contemporaneous cohort of patients with the whole spectrum of acute coronary syndromes, although NT-proBNP has an independent moderate prognostic value for in-hospital cardiovascular mortality, it does not improve the risk stratification prognostic accuracy of the GRACE risk score. But do we need to improve it and add substantial complexity to its use? I do not believe that this is the case.

Keywords

Acute Coronary Syndrome; Heart Failure; Natriuretic Peptide; Factor, Natriuretic Atrial; Mortality; Ventricular Dysfunction, Left; Biomarkers; Brain.

Mailing Address: Ana Teresa Timóteo •
Hospital Santa Marta - Cardiology Department - Rua Santa Marta, 1110. Lisboa – Portugal
E-mail: ana_timoteo@yahoo.com

DOI: https://doi.org/10.36660/abc.20200171

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-2200.
2. Poole-Wilson PA. Who are the enemies? Lack of oxygen. Eur Heart J Suppl. 2002;4(Suppl G):G15-9.
3. Wiese S, Breyer T, Dragu A, Wakili R, Burkard T, Schmidt-Schweda S, et al. Gene expression of brain natriuretic peptide in isolated atrial and ventricular human myocardium: influence of angiotensin 2 and diastolic fiber length. Circulation. 2000;102(25):3074-9.
4. Goetz JP, Christofferson C, Perko M, Arendrup H, Rehfeld JF, Kastrup J, et al. Increase cardiac BNP expression associated with myocardial ischemia. FASEB J. 2003;17(9):1105-7.
5. Morita E, Yasue H, Yoshimura M, Ogawa H, Jougasaki M, Matsumura T, et al. Increased plasma levels of brain natriuretic peptide in patients with acute myocardial infarction. Circulation. 1993;88(1):82-91.
6. Kwan G, Isaksom SR, Beede J, Clopton P, Maisel AS, Fitzgerald RL. Short-term serial sampling of natriuretic peptides in patients presenting with chest pain. J Am Coll Cardiol. 2007;49(11):1186-92.
7. Timóteo AT, Toste A, Ramos R, Miranda F, Ferreira ML, Oliveira JA, et al. Does admission NT-proBNP increases the prognostic accuracy of GRACE risk score in the prediction of short-term mortality after acute coronary syndromes? Acute Card Care. 2009;11(4):236-42.
8. Taiwar S, Squire IB, Downie PF, Mccullough AM, Campton MC, Davies JE, et al. Profile of plasma N-terminal proBNP following acute myocardial infarction; correlation with left ventricular systolic dysfunction. Eur Heart J. 2000;21(18):1514-21.
9. Galvani M, Ottani F, Oltrona L, Ardissino D, Gensini GF, Maggioni AP, et al. N-terminal-pro brain natriuretic peptide on admission has prognostic value across the whole spectrum of acute coronary syndromes. Circulation. 2004;110(2):128-34.
10. Morrow DA, de Lemos JA, Sabatine MS, Murphy SA, Demopoulos LA, DiBattiste PM, et al. Evaluation of B-type natriuretic peptide for risk assessment in unstable angina / non-ST-elevation myocardial infarction: B-type natriuretic peptide and prognosis in TACTICS-TIMI 18. J Am Coll Cardiol. 2003;41(8):1264-72.
11. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al. Predictors of hospital mortality with global registry of acute coronary events. Arch Intern Med. 2003;163(19):2345-53.
12. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(3):267-315.
13. Souza TMB, Cerqueira Jr AMS, Suerdieck JG, Sá NC, Sodré GS, Correia VCA, et al. Prognostic Value of NT-proBNP versus Killip Classification in Patients with Acute Coronary Syndromes. Arq Bras Cardiol. 2020; 114(4):666-672.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

The Relationship Between Epicardial Adipose Tissue and Insulin Resistance in Obese Children

Hatice Güneş,[1] Hakan Güneş,[2] Fatih Temiz[3]

Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Pediatrics,[1] Kahramanmaras – Turquia
Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Cardiology,[2] Kahramanmaraş – Turquia
Kahramanmaras Sutcu Imam University, Faculty of Medicine, Department of Pediatric Endocrinology and Metabolism,[3] Kahramanmaras – Turkey

Abstract

Background: Insulin resistance (IR) is an important disorder in obese children because it is closely related to cardiovascular diseases. Epicardial adipose tissue (EAT) plays a role in the development of IR due to secreted bioactive molecules, and the inflammatory process of these molecules may cause atrial electromechanical delay (EMD).

Objective: The objective of our study was to determine the relationship between EAT and EMD with IR in obese children.

Methods: Ninety-four obese patients were included in the study. IR was calculated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and defined as HOMA-IR greater than the 90th percentile in an age- and sex-specific percentile curve. Patients were divided into two groups according to their IR. All patients underwent echocardiographic examinations. Statistical significance was set to a two-sided p-value < 0.05.

Results: EAT was significantly higher in the IR group (p < 0.001). The optimal cut-off value for EAT to predict IR was found to be > 3.85 mm, with 92.5% specificity and 68.5% sensitivity (p = 0.002). In the multivariate logistic regression model, EAT (OR = 1.256, 95% CI: 1.016–1.53, p = 0.035) was also associated with IR after adjustment for variables found to be statistically significant in univariate analysis. Inter- and intra-atrial EMD was significantly prolonged in the IR group compared to the group without IR (p < 0.010; p = 0.032 respectively).

Conclusion: In our study, we revealed that EAT was positively correlated with IR and was an independent predictor of IR. (Arq Bras Cardiol. 2020; 114(4):675-682)

Keywords: Pericardium; Adipose Tissue; Obesity; Child; Insulin Resistance; Echocardiography/methods.

Introduction

Obesity is a major health problem worldwide due to its growing prevalence and early development in life.[1-3] The number of overweight people tends to progressively increase in both developed and developing countries, and the proportion of obese people is around one third of the normal adolescents population.[4-6] As a result, complications of obesity, such as metabolic syndrome, type 2 diabetes mellitus (DM), cardiovascular disorders, respiratory disorders, and psychosocial problems tend to increase.[7,8]

Obesity is typically associated with insulin resistance (IR) and glucose metabolism disorders. Adipose tissue stored in subcutaneous and visceral tissues plays an important role in the development of IR via the active proteins it secretes.[9] The distribution of this adipose tissue is equally important, with intra-abdominal fat accumulation being closely linked to IR.[10] Additionally, it is already known that subcutaneous fat tissue is correlated to IR whether or not DM is present.[11,12] Recent studies have demonstrated that extra-abdominal visceral fat deposits like mediastinal and epicardial adipose tissue (EAT) are also related to IR.[9,13,14] The association between obesity-dependent insulin resistance and EAT has not been fully explained.

Childhood obesity is an important risk factor for atrial fibrillation whereas structural remodeling is very important.[15] In many studies, this close relationship was investigated with electromechanical delay (EMD), which is one of these echocardiographic markers defined as the temporal delay between the detected onset of electrical activity and the realization of force in the myocardium. EMD is an indicator of atrial conduction heterogeneity and can also be obtained easily by tissue Doppler imaging (TDI).[16] In addition, it has been demonstrated that EMD is prolonged in diseases associated with insulin resistance.[17,18] However, the relationship between electromechanical delay and insulin resistance in obese patients has not been studied.

The aim of our study was to determine the relationship between EAT and insulin resistance. In addition, the relationship between insulin resistance and electromechanical delay was investigated.

Mailing Address: Hakan Gunes •
Sutcu Imam University, Faculty of Medicine, Department of Cardiology. Avşar Mah, Batı Çevreyolu Blv 251/A. Postal Code: 46000, Kahramanmaras – Turkey
E-mail: drhakangunes83@hotmail.com
Manuscript received March 26, 2019, revised manuscript June 12, 2019, accepted June 23, 2019

DOI: https://doi.org/10.36660/abc.20190197

Methods

Study Population

For this prospective and cross-sectional study, 94 obese patients aged 8–18 years admitted to the Kahramanmaraş Sütçüimam University Pediatric Endocrinology outpatient clinic between August 2018 and February 2019 were included. An outpatient clinic nurse performed all anthropometric measurements, including weight and height with the patients wearing underwear only. Body mass index (BMI) was calculated by dividing body weight into kilograms by the square of height in meter. Obesity was defined as BMI greater than the 95th percentile in an age- and sex-specific percentile curve. A value above the 99th percentile was defined as morbid obesity.[19]

All patients' insulin resistance was calculated, and they were categorized on the basis of insulin resistance. Insulin resistance was calculated using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) (fasting plasma glucose (mmol/L) × fasting plasma insulin (mU/L)/22.5) and defined as HOMA-IR greater than the 90th percentile in an age- and sex-specific percentile curve.[20]

Patients with DM, Cushing Syndrome, known insulin resistance; those using drugs for insulin resistance; those having hypoglycemia; those with known metabolic cardiovascular and hepatic disorders; and those with poor acoustic windows for echocardiography were excluded. Demographic and laboratory data of the patients were recorded. All patients underwent standard transthoracic echocardiography including tissue Doppler examination and echocardiographic examinations were performed by an expert cardiologist. The same cardiologist evaluated pre-discharge TTE results of 20 randomly selected patients to assess the reproducibility of EAT thickness and tissue Doppler parameters for atrial electromechanical delay. Using the Bland-Altman method, the mean difference in terms of intra-observation was 3.8% (0.23 ± 0.54%), indicating good reproducibility.

Echocardiography

Transthoracic echocardiographic examinations were performed by expert echocardiographers who were blind to the patients' clinical information with the Vivid 7® cardiac ultrasonography system (GE VingMed Ultrasound AS; Horten, Norway) using 2.5- to 5-MHz probes. The echocardiographic images were taken in left lateral and supine positions and 2D, M-mode, pulsed, and color flow Doppler echocardiography examinations were performed in every patient. Parasternal long and short axes, apical and subcostal windows were used to obtain Doppler tracings and two-dimensional images. Left and right atrial diameters left ventricular end-systolic and end-diastolic diameters, as well as the posterior and septal wall thicknesses of the left ventricle at diastole, were quantified. Left atrial volumes were quantified with the disc method LV ejection fraction (EF) with the Simpson's rule. LV diastolic function was quantified using mitral inflow velocities, i.e. peak E (early diastolic), peak A (late diastolic), E/A ratio as well as E-wave (DT) deceleration time and isovolumic relaxation time (IVRT).

Echocardiographic assessment and quantification of epicardial fat were done by identifying the echo-free space between the outer lining of the myocardium and the visceral layer of pericardium. Its measurement was made perpendicular to the free wall of the right ventricle in the parasternal long-axis window. The measurement level was at the mid ventricle and the timing was set to end-diastole, with an average of 3 cardiac cycles being taken. To align the ultrasound beam perpendicular to the right ventricular free wall, aortic annulus was accepted as the anatomic landmark.[21]

Tissue Doppler Echocardiography (TDE)

The pulsed Doppler sample volume was placed at the level of LV lateral mitral annulus, septal mitral annulus, and RV tricuspid annulus from an apical four-chamber view. The time interval from the onset of the P-wave on surface ECG to the beginning of the late diastolic wave (Am), which is called PA, was taken from the lateral mitral annulus (lateral PA), septal mitral annulus (septal PA), and RV tricuspid annulus (tricuspid PA). The difference between septal PA and tricuspid PA (septal PA − tricuspid PA) was identified as an intra-atrial electromechanical delay while the difference between lateral PA and tricuspid PA (lateral PA − tricuspid PA) was identified as inter-atrial electromechanical delay.[16]

Statistical Analysis

All statistical analyses were performed using the SPSS version 14 (SPSS Inc., Chicago, IL, USA) software package. Statistical significance was set to a two-sided p-value < 0.05. Categorical variables were expressed as number and percentage while continuous variables as mean±standard deviation (SD) or median and interquartile ranges (IQR), depending on their normality of distribution. The normality assumption of the data was determined using the Kolmogorov Smirnov test. The independent sample t-test and Mann–Whitney U test were used to compare the groups' means. The Chi-square test was used to compare categorical data. Correlation analyses were performed using the Pearson correlation test for normally distributed variables and Spearman correlation test for non-normally distributed variables. An optimal cut-off point was determined for EAT to predict IR using the receiver operator characteristic (ROC) curve analysis MedCalc (v12.7.8). This was accomplished by determining the area under the curve (AUC) with 95% confidence interval. The best cutoff value for EAT was determined by calculating the highest sum of sensitivity and specificity-1. The IR and available variables were analyzed for correlation using the univariate analysis. Variables with significant correlation in the univariate analysis were entered in the multivariate logistic regression model using the backward stepwise method along with other potential confounders to determine independent predictors of IR.

Results

Enrolled patients were divided into two groups based on the presence of insulin resistance. Forty patients had insulin resistance and 54 patients did not. Both groups had similar age and gender distribution. ($p = 0.102$, $p = 0.069$, respectively). Among the anthropometric measurements, weight, height, and

BMI were significantly greater in patients with insulin resistance. Additionally, diastolic and systolic blood pressure measurements were significantly greater in the IR group. A comparison of laboratory parameters revealed that the IR group had significantly higher serum insulin and glucose levels ($p < 0.001$, $p = 0.002$, respectively). The other laboratory parameters were similar between the groups (Table 1). Among standard echocardiographic measurements, EAT thickness was significantly increased in the group with IR ($p = 0.004$). Other standard echocardiographic and laboratory parameters were similar between the two groups. Atrial electromechanical delays recorded from different annular segments are given in Table 2. Lateral and septal PA was significantly higher in the IR group (62.2 ± 8.3 vs. 56.6 ± 8.4, $p = 0.002$; 46.1 ± 6.1 vs. 42.7 ± 5.9, $p = 0.019$ respectively). Tricuspid PA was similar between the groups. Inter- and intra-atrial EMD was significantly prolonged in the IR group compared to the group without insulin resistance (23 (18–30) vs. 19.5 (15–23.5), $p < 0.010$; 9.5 (6.2–10.0) vs. 6 (4–9.2), $p = 0.032$, respectively)

The echocardiographic parameters that showed correlations with HOMA-IR are summarized in Table 3. EAT thickness, inter- and intra-atrial EMD, lateral and septal PA were positively correlated to HOMA-IR.

The best cut-off value for EAT for the prediction of insulin resistance was >3.85 mm, with 92.5% specificity and 68.5% sensitivity (AUC = 0.672; 95% CI, 0.563–0.781; $p = 0.002$ (Figure 1).

In the multivariate logistic regression model using the backward stepwise method, EAT thickness (OR = 1.256, 95% CI: 1.016–1.53, p=0.035) and SBP (OR = 1.039, 95% CI: 1.007–1.072, $p = 0.015$) still remained significant predictors of IR after adjusting for the confounding variables, which were both found to be statistically significant in the univariate analysis (Table 4).

Discussion

This study investigated the relationship between epicardial adipose tissue and insulin resistance among obese children. It has been shown that epicardial adipose tissue is positively correlated to IR and an independent predictor of IR.

IR denotes a condition of relative insensitivity of peripheral tissues (e.g. muscle, liver, and adipose tissue) to the effects of the hormone. IR plays a pivotal role in the development and progression of cardio-metabolic risk factors that, in association with obesity, due to lipolytic effects of adipocytes, leading to large amounts of free fatty acids and impaired secretion of adipokines, both involved in the modulation of insulin sensitivity.[20-22] Although the prevalence of IR is variable among obese patients, Gabato et al. reported it to be 29.1% in their study.[23] In many other studies, this rate has been shown to be over 50%.[24-27] In our study, the rate of IR was found to be 43%. The reason for this difference can be explained by the use of constant HOMA-IR value in other studies, but, in our study, we used HOMA-IR percentile values according to age and gender.

The HOMA-IR is a proxy estimate of IR based upon the relationship between fasting glucose and insulin levels, with higher values of HOMA-IR representing more severe IR.[10] Increased IR and HOMA-IR values increase cardio-metabolic risk. There is no evidence of an association between IR measures and incident AF.[28] Many studies have shown that IR is closely related to atrial functions.[29,30] In our study, it was observed that HOMA-IR values were positively correlated with atrial tissue Doppler parameters which are indicative of atrial function in obese children and tissue atrial conduction was increased in the IR group.

Obesity causes prolongation of electromechanical conduction time by many mechanisms such as fat inflammation on the atrial wall, increase in sympathetic nervous system activity, increased inflammatory process, adipokinin dysregulation and activation of pro-fibrotic signaling pathways. Electromechanical conduction prolongation has been shown to be prone to atrial fibrillation.[31] IR, which is frequently associated with obesity, has an effect on atrial functions due to existing subclinical inflammation. In our study, both intra- and inter-atrial conduction time was found to be higher in obese children with insulin resistance, according to the literature, compared to the non-IR group. This may be explained by the inflammatory process associated with insulin resistance and by the delayed transmission of this inflammatory process on the atrial tissue. In the light of this information, it can be said that obese children who have insulin resistance may be more prone to atrial fibrillation.

Epicardial fat is a visceral fat accumulation that has most of the pathophysiological properties of other visceral adipose tissues, like lipid deposition and release of hormones, cytokines, and chemokines; and it also causes local inflammation.[32-35] It has been shown that body fat distribution, particularly abdominal fat distribution, is correlated with epicardial adipose tissue.[33] Hence, the relationship between epicardial adipose tissue thickness obtained from echocardiography and a number of pathological conditions such as metabolic syndrome, coronary artery disease, hyperlipidemia, blood pressure elevation, and IR has been studied in obese adult and pediatric patients. Epicardial adipose tissue causes the development and/or worsening of IR by increasing free fatty acids, TNF, IL1, IL6, and resistin release and decreasing adiponectin levels.[36] Several studies that examined the relationship between epicardial adipose tissue and IR demonstrated a correlation between epicardial adipose tissue and BMI in obese adults.[37-39] Abacı et al. showed a significant correlation with epicardial fatty tissue among obese children.[40] In line with the literature available, our study demonstrated a correlation between BMI and epicardial fatty tissue. Ishorbagy et al. reported that epicardial fatty tissue was larger in amount in obese patients than in healthy controls, although it did not predict metabolic syndrome.[41] Similarly, Abacı et al. suggested that epicardial fatty tissue failed to predict IR among obese children.[40] On the other hand, we found that epicardial fatty tissue was an independent predictor of IR. The cause of this discrepancy is that our study was a nested case-control study that only included patients instead of healthy controls. Another important reason was that in our study, IR was taken using determined percentiles according to age and gender.

The relationship between arterial blood pressure and IR has been shown in many studies [42,43] In our study, we found that systolic blood pressure is an independent predictor of IR. This may be due to increased fat tissue in the body that plays an important role in IR and subclinical inflammation caused

Table 1 – Baseline characteristics of study patients

	Obese patients with insulin resistance (n = 40)	Obese patients without insulin resistance (n = 54)	p
Age, median (IQR), years	13 (11–16)	12 (9–15)	0.102
Height, median (IQR), m	1.65 (1.55–1.70)	1.60 (1.43–1.65)	0.009
Weight, mean ± SD, kg	83.47 ± 21.22	64.13 ± 18.24	< 0.001
BMI, median (IQR)	31.8 (28.1–36.9)	29.7 (25–32.3)	0.019
Female/male (n)	20/20	37/17	0.069
SBP, median (IQR), mmHg	110 (100–130)	100 (80–130)	0.003
DBP, median (IQR), mmHg	80 (70–90)	70 (60–80)	0.016
Heart rate, mean ± SD, beats/min	72 ± 6	72 7	0.945
Laboratory findings			
Blood glucose, mean ± SD, mg/dL	92 ± 8	87 ± 6	0.002
Insulin, median (IQR), µIU/L	32.5 (24.6–42.7)	13.6 (10.4–16.8)	< 0.001
HbA1C, median (IQR), %	5.5 (5.2–5.6)	5.4 (5.1–5.6)	0.590
Urea, mean ± SD, mg/dL	9.9 ± 3.2	9.5 ± 1.9	0.606
ALT median (IQR), U/L	25 (16–34)	22 (17–28)	0.167
AST mean ± SD, U/L	24.9 ± 8.7	25.3 ± 7.5	0.807
Total Protein, median (IQR), g/dL	7.6 (7.3–7.9)	7.6 (7.2–8.0)	0.672
Albumin, mean ± SD,	4.7 ± 0.2	4.8 ± 0.4	0.577
Triglycerides, median (IQR), mg/dL	131 (112–155)	118 (90–154)	0.289
Total cholesterol, mean ± SD, mg/dL	171.2 ± 32.3	160.6 ± 21.5	0.079
HDL cholesterol, mean ± SD, mg/dL	41.8 ± 9.0	41.0 ± 8.7	0.686
LDL cholesterol, median (IQR), mg/ dL	89.5 (73.2–113.7)	86.5 (73–104.5)	0.491
TSH, median (IQR), mIU/L	2.55 (1.15–3.16)	2.79 (2.06–3.87)	0.061
T4, median (IQR), ng/dL	1.21 (1.13–1.33)	1.17 (1.06–1.30)	0.172
Cortisol, mean ± SD, µg/Dl	10.4 ± 6.4	10.0 ± 4.8	0.760
WBC, median (IQR), $x10^3/mm^3$	8330 (7232–10150)	8385 (7365–9900)	0.921
Hemoglobin, mean ± SD, g/dL	13.8 ± 0.9	13.5 ± 1.0	0.171
Platelet count, mean ± SD, $10^3/mm^3$,	333 ± 77	340 ± 72	0.595
RDW, median (IQR), %	13.6 (13.1–14.2)	13.4 (12.8–14.0)	0.147
Echocardiographic parameters			
EF, median (IQR), %	70 (70–72)	72 (70–72)	0.667
LVDD, mean ± SD, mm	4.3 ± 0.5	4.1 ± 0.4	0.059
LVSD, mean ± SD, mm	3.3 ± 0.6	3.2 ± 0.5	0.329
LA diameter, median (IQR), cm	3.0 (3.0–3.4)	3.1 (3.0–3.3)	0.792
RA diameter, mean ± SD, mm	3.3 ± 0.5	3.2 ± 0.5	0.165
RV thickness, median (IQR), cm	0.50 (0.42–0.60)	0.50 (0.40–0.55)	0.121
RV diameter, median (IQR), mm	2.7 (2.4–3.0)	2.5 (2.2–2.8)	0.176
Posterior wall thickness, median (IQR), mm	0.80 (0.70–0.90)	0.70 (0.70–0.80)	0.111
Septal thickness, median (IQR), mm	0.80 (0.70–0.90)	0.70 (0.70–0.90)	0.664
Epicardial adipose tissue, median (IQR), mm	7.15 (5.5–8.8)	5.5 (3.3–7.7)	0.004

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HbA1c: hemoglobin A1c; ALT: alanine aminotransferase; AST: aspartate aminotransferase; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TSH: thyroid stimulating hormone; RDW: red cell distribution width; EF: ejection fraction; LVDD: left ventricle end diastolic dimension; LVSD: left ventricle end systolic dimension; LA: LEFT atrium; RA: right atrium; RV: right ventricle; WBC: white blood cell. Data are presented as mean±standard deviation (SD), number and percentage, or median and interquartile ranges (IQR). p < 0.05 was considered statistically significant.

Table 2 – Comparison of atrial electromechanical delay parameters measured by tissue Doppler imaging

	Obese patients with insulin resistance (n = 40)	Obese patients without insulin resistance (n = 54)	p
Lateral PA, mean±SD, ms	62.2 ± 8.3	56.6 ± 8.4	0.002
Septal PA, mean ± SD, ms	46.1 ± 6.1	42.7 ± 5.9	0.019
Tricuspid PA, mean ± SD, ms	38.0± 5.8	36.1 ± 4.7	0.088
Inter-atrial EMD, median (IQR), ms	23 (18–30)	19.5 (15–23.5)	0.010
Intra-atrial EMD, median (IQR), ms	9.5 (6.2–10.0)	6 (4–9.2)	0.032

PA: Time interval from the onset of P-wave on surface ECG to the beginning of Am wave interval with tissue Doppler echocardiography; EMD: Electromechanical delay, IQR: Interquartile ranges.

Table 3 – Echocardiographic parameters that correlate with HOMA-IR

Variables Correlating with HOMA-IR		
	R	P
Epicardial adipose tissue	0.422	< 0.001
Inter-atrial EMD	0.360	< 0.001
Intra-atrial EMD	0.345	0.001
Lateral PA	0.451	< 0.001
Septal PA	0.305	0.001

HOMA-IR: homeostatic model assessment for insulin resistance; PA: time interval from the onset of P-wave on surface ECG to the beginning of Am wave interval with tissue Doppler echocardiography; EMD: electromechanical delay.

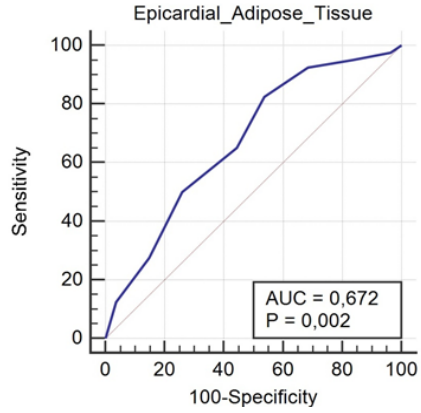


Figure 1 – *Receiver operator characteristic (ROC) curve of EAT to predict insulin resistance.*

by inflammatory cytokines, such as IL-6, IL-1 and TFN-alpha secreted from this adipose tissue. Subclinical inflammation can both impair endothelial function and increase blood pressure by decreasing NO release. Another possible mechanism is: there may be sympathetic activation of both the obesity and the obesity-related inflammatory process.[36,44-47]

Our study had some limitations: its main limitation was the relatively small sample size. Echocardiographic EAT is a linear measurement. Thus, it may not assess the total epicardial fat volume that varies at several myocardial locations. As a result of EAT, metabolically active tissue, inflammatory cytokines and inflammatory markers could be investigated in future studies. The absence of waist circumference measurement was another limitation, precluding the determination of a relationship between waist circumference and epicardial fat.

Conclusion

In conclusion, epicardial adipose tissue is a cheap, easily accessible parameter that can be easily measured with echocardiography and used to identify insulin resistance among children. Since atrial electromechanical delay increased in obese children with insulin resistance, it should be followed closely for atrial fibrillation.

Table 4 – Univariate and multivariate analysis for predicting insulin resistance

	Univariate Analysis						Multivariate Analysis					
	B	S.E.	Wald	P	OR	%95 CI	B	S.E.	Wald	P	OR	%95 CI
Epicardial adipose tissue	0,275	0,098	7,886	0,005	1,317	1,087–1,596	0,228	0,108	4,423	0,035	1,256	1,016–1.553
Systolic blood pressure	0,044	0,015	8,384	0,004	1,045	1,014–1,077	0,038	0,016	5,896	0,015	1,039	1,007–1.072
Diastolic blood pressure	0,049	0,019	6,959	0,008	1,050	1,013–1,089						
PA Lateral	0,078	0,027	8,661	0,003	1,081	1,026–1,139						
PA Septum	0,095	0,038	6,386	0,012	1,100	1,022–1,184						
Inter-atrial EMD	0,066	0,029	5,123	0,024	1,068	1,009–1,130						
Intra-atrial EMD	0,149	0,065	5,352	0,021	1,161	1,023–1,318						
Height	3,845	1,671	5,292	0,021	46,737	1,767–1236,369						
Weight	0,032	0,011	8,804	0,003	1,033	1,011–1,055						

All the variables from Table 1 and Table 2 were examined and only those significant at p < 0.05 level are shown in univariate analysis. Multivariate logistic regression analyses including all the variables in univariate analysis with the enter method. p < 0.05 was considered statistically significant. Non-significant variables in the multivariate logistic regression analysis were not included in table. B: Beta coefficients; CI: Confidence interval; EMD: Electromechanical delay. OR: odds ratio; PA: time interval from the onset of P-wave on surface ECG to the beginning of Am wave interval with tissue Doppler echocardiography; S.E.: standard error; Wald: Wald test.

Author contributions

Conception and design of the research: Güneş H; Acquisition of data and Statistical analysis: Güneş, H, Temiz F; Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Güneş H, Güneş, H, Temiz 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.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Kahramanmaraş Sütçü İmam University under the protocol number 349/2019. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all patients participants included in the study.

References

1. World Health Organization. (WHO). "Global and regional trends by UN Regions, 1990–2025; Overweight:1 990-2015". Genrva;2016. [Cited in 2018 Jan 10] Available from: http://apps.who.int/gho/data/node.main.NUTUNREGIONS?
2. Lobstein T, Jackson-Leach R, Moodie ML, Hall KD, Gortmaker SL, Swinburn BA,et al. Child, and adolescent obesity: part of a bigger picture. Lancet. 2015;385(9986):2510-20.
3. de Onis M, Blössner M, Borghi E. Global prevalence and trends of overweight and obesity among preschool children. Am J Clin Nutr. 2010;92(5):1257-64.
4. Ogden CL, Carroll MD, Kit BK, Flegal KM. Prevalence of childhood and adult obesity in the United States, 2011-2012. JAMA. 2014;311(8):806-14.
5. Strauss RS, Bradley LJ, Brolin RE. Gastric bypass surgery in adolescents with morbid obesity. J Pediatr. 2001;138(4): 499-504.
6. Roberto CA, Swinburn B, Hawkes C, Huang TT, Costa SA, Ashe M, et al. Patchy progress on obesity prevention: emerging examples, entrenched barriers, and new thinking. Lancet. 2015;385(9985):2400-9.
7. Han JC, Lawlor DA, Kimm SY. Childhood obesity. Lancet.2010;375(9727):1737-48.
8. Kelly AS, Barlow SE, Rao G, Inge TH, Hayman LL, Steinberger J, et al. American Heart Association Atherosclerosis, Hypertension, and Obesity in the Young Committee of the Council on Cardiovascular Disease in the Young, Council on Nutrition, Physical Activity and Metabolism, and Council on Clinical Cardiology. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. Circulation. 2013 8;128(15):1689-712.
9. Iacobellis G, Leonetti F. Epicardial adipose tissue and insulin resistance in obese subjects. J Clin Endocrinol Metab. 2005 ;90(11):6300-2.
10. Mazur A, Ostański M, Telega G, Malecka-Tendera E. Is epicardial fat tissue a marker of metabolic syndrome in obese children? Atherosclerosis. 2010;211(2):596-600.
11. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM. Relationships of generalized and regional adiposity to insulin sensitivity in men. J Clin Invest.1995;96(1):88-98.

12. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Adams-Huet B, Grundy SM. Relationship of generalized and regional adiposity to insulin sensitivity in men with NIDDM. Diabetes. 1996;45(12):1684-93.

13. Chandalia M, Abate N, Garg A, Stray-Gundersen J, Grundy SM. Relationship between generalized and upper body obesity to insulin resistance in Asian Indian men. J Clin Endocrinol Metab.1999;84(7):2329-35.

14. Sharma AM. Mediastinal fat, insulin resistance, and hypertension. Hypertension. 2004;44(2):117-8.

15. El-Assaad I, Al-Kindi SG, Saarel EV, Aziz PF. Lone pediatric atrial fibrillation in the United States: analysis of over 1500 cases. PediatrCardiol. 2017;38(5):1004–9.

16. Gunes H, Sokmen A, Kaya H, Gungor O, Kerkutluoglu M, Guzel FB, et al. Evaluation of Atrial Electromechanical Delay to Predict Atrial Fibrillation in Hemodialysis Patients. Medicina (Kaunas). 2018; 54(4): E58.

17. Kurt M, Tanboğa IH, Karakaş MF, Büyükkaya E, Akcay AB, Sen N, et al. The relationship between atrial electromechanical delay and P-wave dispersion with the presence and severity of metabolic syndrome. Turk Kardiyol Dern Ars. 2012;40(8):663-70.

18. Zehir R, Karabay CY, Kocabay G, Kalayci A, Kaymaz O, Aykan AC, et al. Assessment of atrial conduction time in patients with polycystic ovary syndrome. J Interv Card Electrophysiol.2014;41(2):137-43.

19. Barlow SE. Expert Committee recommendations re¬garding the prevention, assessment, and treatment of child and adolescent overweight and obesity: summary report. Pediatrics. 2007;120(suppl 4); p164-92.

20. Shashaj B, Luciano R, Contoli B, Morino GS, Spreghini MR, Rustico C, et al. Reference ranges of HOMA-IR in normal-weight and obese young Caucasians. Acta Diabetol. 2016;53(2):251-60.

21. Iacobellis G., Lonn E., Lamy A. Epicardial fat thickness and coronary artery disease correlate independently of obesity. Int J Cardiol. 2011;146(3):452–4.

22. Castro AV, Kolka CM, Kim SP, Bergman RN. Obesity, insulin resistance, and comorbidities? Mechanisms of association. Arq Bras Endocrinol Metabol.2014;58(6):600-9.

23. Gobato AO, Vasques AC, Zambon MP, Barros Filho A, Hessel G. Metabolic syndrome and insulin resistance in obese adolescents. Rev Paul Pediatr. 2014;32(1):55-62.

24. Keskin M, Kurtoglu S, Kendirci M, Atabek ME, Yazici C. Homeostasis model assessment is more reliable than the fasting glucose/insulin ratio and quantitative insulin sensitivity check index for assessing insulin resistance among obese children and adolescents. Pediatrics. 2005;115:e500–3.

25. Souza MS, Leme RB, Franco RR, Romaldini CC, Tumas R, Cardoso AL, et al. Metabolic syndrome in obese and overweight adolescents. Rev Paul Pediatr. 2007;25:214–20.

26. Juárez-López C, Klünder-Klünder M, Medina-Bravo P, Madrigal-Azcárate A, Mass-Díaz E, Flores-Huerta S. Insulin resistance and its association with the components of the metabolic syndrome among obese children and adolescents. BMC Public Health. 2010 Jun 07;10:318

27. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412–9.

28. Cho ME, Craven TE, Cheung AK, Glasser SP, Rahman M, Soliman EZ, et al. SPRINT Study Research Group. The association between insulin resistance and atrial fibrillation: A cross-sectional analysis from SPRINT (Systolic Blood Pressure Intervention Trial). J Clin Hypertens (Greenwich). 2017;19(11):1152-61.

29. Nyman K, Granér M, Pentikäinen MO, Lundbom J, Hakkarainen A, Sirén R, et al. Metabolic syndrome associates with left atrial dysfunction. Nutr Metab Cardiovasc Dis. 2018;28(7):727-34.

30. De Sensi F, Costantino S, Limbruno U, Paneni F. Atrial fibrillation in the cardiometabolic patient. Minerva Med. 2019;110(2):157-67.

31. Temız F, Gunes H, Gunes H. Evaluation of atrial electromechanical delay in children with obesity Medicina (Kaunas). 2019; 55(6): E228.

32. Gastaldelli A, Basta G. Ectopic fat and cardiovascular disease: what is the link? Nutr Metab Cardiovasc Dis. 2010; 20(7):481–90.

33. Iacobellis G, Corradi D, Sharma AM. Epicardial adipose tissue: anatomic, biomolecular and clinical relationships with the heart. Nat Clin Pract Cardiovasc Med. 2005;2(10):536-43.

34. Schejbal V. Epicardial fatty tissue of the right ventricle F morphology, morphometry, and functional significance. Pneumologie. 1989;43(9):490-9.

35. Marchington JM, Mattacks CA, Pond CM. Adipose tissue in the mammalian heart and pericardium: structure, foetal development and biochemical properties. Comp Biochem Physiol B.1989;94(2):225-32.

36. Iacobellis G, Ribaudo MC, Assael F, Vecci E, Tiberti C, Zappaterreno A et al. Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: a new indicator of cardiovascular risk. J Clin Endocrinol Metab. 2003;88(11):5163-8.

37. Iacobellis G, Leonetti F. Epicardial adipose tissue and insulin resistance in obese subjects. J Clin Endocrinol Metab. 2005;90(11):6300-2.

38. Cikim AS, Topal E, Harputluoglu M, Keskin L, Zengin Z, Cikim K, et al. Epicardial adipose tissue, hepatic steatosis and obesity. J Endocrinol Invest. 2007; 30(6):459-64.

39. Okyay K, Balcioglu AS, Tavil Y, Tacoy G, Turkoglu S, Abaci A. A relationship between echocardiographic subepicardial adipose tissue and metabolic syndrome. Int J Cardiovasc Imaging. 2008;24(6):577-83.

40. Abaci A, Tascilar ME, Saritas T, Yozgat Y, Yesilkaya E, Kilic A,et al. Threshold value of subepicardial adipose tissue to detect insulin resistance in obese children. Int J Obes (Lond). 2009;33(4):440-6.

41. Elshorbagy HH, Fouda ER, Kamal NM, Bassiouny MM, Fathi WM. Evaluation of Epicardial Fat and Carotid Intima-Media Thickness in Obese Children. Iran J Pediatr. 2016;26(1):e2968.

42. Wu X, Han T, Gao J, Zhang Y, Zhao S, Sun R,et al. Association of Serum Calcium and Insulin Resistance With Hypertension Risk: A Prospective Population-Based Study. J Am Heart Assoc.2019;8(1):e009585.

43. Bamaiyi AJ, Woodiwiss AJ, Peterson V, Gomes M, Libhaber CD, Sareli P,et al. Insulin resistance influences the impact of hypertension on left ventricular diastolic dysfunction in a community sample. Clin Cardiol.2019;42(2):305-11.

44. Gastaldelli A, Morales MA, Marraccini P, Sicari R. The role of cardiac fat in insulin resistance. Curr Opin Clin Nutr Metab Care. 2012;15(6):523-8.

45. Solak Y, Afsar B, Vaziri ND, Aslan G, Yalcin CE, Covic A, et al. Hypertension as an autoimmune and inflammatory disease. Hypertens Res. 2016;39(8).567–73.

46. Jansen van Vuren E, Malan L, von Känel R, Lammertyn L, Cockeran M, Malan NT. Longitudinal changes of cardiac troponin and inflammation reflect progressive myocyte stretch and likelihood for hypertension in a Black male cohort: The SABPA study. Hypertens Res. 2019 ;42(5):708-16.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Galectin-3 Levels in Patients with Chronic Constrictive Pericarditis

Fábio Fernandes,[1,2] Dirceu Thiago Pessoa de Melo,[1] Felix José Alvarez Ramires,[1,2] Ester Cerdeira Sabino,[3] Carlos Henrique Valente Moreira,[4] Luiz Alberto Benvenutti,[1,2] Viviane Tiemi Hotta,[1,2] Ana Luiza Carrari Sayegh,[2] Francis Ribeiro de Souza,[2] Ricardo Ribeiro Dias,[1,2] Charles Mady[1,2]

Instituto do Coração HC-FMUSP - Unidade Clínica de Miocardiopatias e Doenças da Aorta,[1] São Paulo, SP – Brazil
Universidade de São Paulo Faculdade de Medicina Hospital das Clínicas Instituto do Coração,[2] São Paulo, SP – Brazil
Universidade de São Paulo - Instituto de Medicina Tropical de São Paulo São Paulo,[3] São Paulo, SP – Brazil
Emilio Ribas Institute for Infectious Diseases,[4] São Paulo, SP – Brazil

Abstract

Background: **Galectin-3 (Gal-3) is a proinflammatory, profibrotic molecule implicated in the pathogenesis of heart failure. The role of Gal-3 in patients with chronic constrictive pericarditis (CCP) is not clear.**

Objective: **The aim of this study was to assess plasma Gal-3 in patients with CCP and correlate it with clinical, functional and histologic parameters.**

Methods: **We prospectively evaluated 25 symptomatic patients with CCP referred for pericardiectomy and 21 healthy controls. Patients underwent clinical assessment, Gal-3 and B-type natriuretic peptide (BNP) measurements, echocardiography, cardiac magnetic resonance imaging and cardiopulmonary exercise test (CPET) at baseline. Six months after pericardiectomy CPET was repeated. An alpha error < 5% was considered statistically significant, with a confidence interval of 95%.**

Results: **Twenty-five patients with a median age of 45 years were included. Etiology was mainly idiopathic (n = 19, 76%); and 14 (56%) patients had NYHA functional class III/IV. Median BNP and Gal-3 were 143 (89-209) pg/dL and 14.8 (9.7-17.2) ng/mL, respectively. Gal-3 levels were not significantly higher in CCP patients than in control (p = 0.22). There were no significant correlations of Gal-3 with BNP, echocardiographic and cardiac magnetic resonance measures and histological findings. After pericardiectomy, it was found a statistically significant correlation between Gal-3 and the CPTE measures test duration (r = –0.79; p < 0.001) and exercise time (r = –0.79; p < 0.001).**

Conclusions: **Patients with CCP had normal levels of Gal-3 as compared to the controls. Gal-3 did not correlate with morphological and functional measures before pericardiectomy. However, the associations between Gal-3 and exercise intolerance after pericardiectomy may suggest a role of Gal-3 in prognosis prediction after pericardiectomy. (Arq Bras Cardiol. 2020; 114(4):683-689)**

Keywords: **Pericardite Constrictive/surgery; Galectin 3; Cell Diferentiation; Pericardiectomy/methods; Fibrosis.**

Introduction

Patients with chronic constrictive pericarditis (CCP) have pericardial thickness that leads to restriction of diastolic filling of the ventricles. Clinical presentation of CCP is usually indolent and nonspecific in the early stages. Symptoms are attributable to biventricular diastolic dysfunction and include fatigue and decreased exercise tolerance.[1]

The progression of pericardial inflammation is a continuous event. Pericardial constriction after acute pericarditis seems to be related to fibroblast proliferation and fibrinous exudate, resulting in a thickened and inelastic pericardium.[2] However, the mechanisms underlying pericardial fibrosis and calcification in CCP remain poorly understood.

Galectin-3 (Gal-3), a beta-galactosidase binding lectin, is secreted by activated macrophages and is involved in the fibrogenesis process. Gal-3 is also a strong proinflammatory mediator.[3,4]

Limited data are available on galectin levels in patients with pericardial disease. In a pilot study, Ntsekhe et al.[5] studied patients with normal pericardium and patients with tuberculous pericarditis to define the levels of endogenous Ac-SDKP (N-acetyl-seryl-aspartyl-lysyl-proline) and Gal-3 in normal pericardial fluid. They found that AcSDKP, a tetrapeptide with antifibrotic properties, and Gal-3 are detectable in normal pericardial fluid, and that tuberculous pericarditis was associated with low levels of pericardial AcSDKP and normal Gal-3 levels. Nevertheless, the role of Gal-3 in patients with CPP is not clear.

Given the role of pericardial inflammation and fibrosis in the pathogenesis of CCP, we hypothesized that Gal-3 may

Mailing Address: Dirceu Thiago Pessoa de Melo •
Universidade de São Paulo Faculdade de Medicina Hospital das Clínicas Instituto do Coração - Dr. Eneas de Carvalho Aguiar, 44. Postal Code 05403-000, São Paulo, SP – Brazil
E-mail: dirceumelo@yahoo.com.br
Manuscript received March 01, 2019, revised manuscript June 11, 2019, accepted June 23, 2019

DOI: https://doi.org/10.36660/abc.20190152

serve as a biomarker or modulator of severity in patients with constrictive pericarditis. The aim of this study was to assess plasma Gal-3 levels in patients with CCP and correlate these levels with functional and histologic parameters.

Methods

Study population

In this prospective study, 33 patients with surgically proven constrictive pericarditis were included. Twenty-nine patients underwent radical pericardiectomy from February 2011 through November 2015 in a tertiary hospital in São Paulo, Brazil. Four patients were excluded from the study by the following exclusion criteria: patients older than 70 years old, severe pulmonary disease according to a lung test, and moderate/severe valvular heart disease. Twenty-five patients were compared with 21 healthy, physically inactive individuals without heart disease (control group). The sample size was defined by convenience. The presumptive diagnosis of CCP was based on clinical, echocardiographic, and cardiac magnetic resonance (CMR) imaging criteria according to European Society of Cardiology guidelines and proven by surgery.[1] The following procedures were performed during hospitalization for surgery: measurement of serum B-type natriuretic peptide (BNP) levels, transthoracic echocardiography, cardiopulmonary exercise test (CPET) and CMR imaging test (Figure 1 depicts the screening process).

Tuberculosis constriction was defined by pericardial biopsy, when caseating granuloma was demonstrated or polymerase chain reaction was positive for *Mycobacterium sp*. Postsurgical constriction was defined as constrictive pericarditis after cardiac surgery. Constriction secondary to systemic inflammatory disease was defined in two patients with lupus erythematosus. Idiopathic constriction was defined when patients did not qualify for any of the previous groups.

Study design

This was a case control study with controls (healthy subjects) paired by age and sex.

Procedures

Pericardiectomy procedure

Median sternotomy was performed in all cases without cardiopulmonary bypass. Total pericardiectomy was performed with excision of the pericardium anteriorly, extending to both phrenic nerves and diaphragmatic pericardium. When this procedure was technically impossible, removal of parietal and visceral pericardium was attempted.

Cardiopulmonary exercise test

Functional capacity was evaluated using the CPET, according to American Heart Association guidelines.[6] The evaluation was performed on a treadmill (*Ergoline - Via Sprint 150 P*) with modified Balke protocol with velocity varying from 2 to 3.4 mph and a ramp increment of 2% per minute. After placement on the treadmill, patients were connected to a volume transducer, with nose clipped, electrocardiographic monitoring (*Micromed - Cardio PC 13*) was performed. The oxygen (O_2) and carbon dioxide (CO_2) fractions were measured at each respiratory cycle. This evaluation was performed using a computerized system (*Sensormedics, Vmax Analyzer Assembly, Encore 29S*). Blood pressure was assessed by the auscultatory method, and measurements were taken every two minutes of exercise. In the recovery period, blood pressure was measured in the first, second, fourth, and sixth minutes. The cardiopulmonary exercise test was considered maximum when the individual reached at least one of the following parameters: respiratory exchange ratio > 1.10, heart rate > 95% of predicted for age, and extreme tiredness.

BNP assays were performed using the ADVIA Centaur® Kit (*Siemens Medical Solutions Diagnostic, Los Angeles, California, USA*) and processed in automated equipment of the same brand. Samples were processed within two hours as recommended by the manufacturer.

Plasma Gal-3 levels were determined using an Enzyme-Linked Fluorescent Assay (*ELFA*) and measured on Biomerieux Vidas 30 (*Biomerieux, Marcy l'Etoile, LY-France*). Calibration of the assay was performed according to the manufacturer's recommendations.

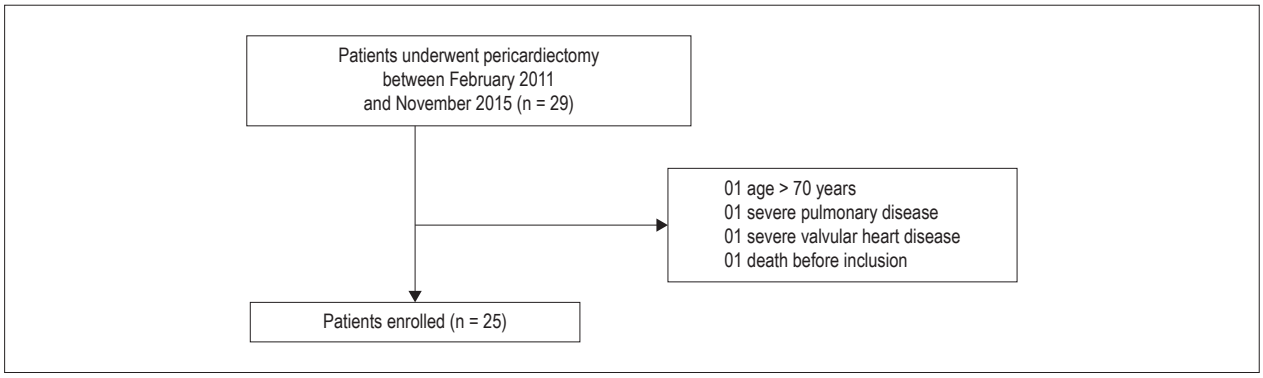


Figure 1 – *Screening process.*

Echocardiography

The echocardiographic study was performed on a Sequoia 512 ultrasound device (*Acuson, Mountain View, California, USA*) with a 2.5 MHz transducer. All measurements were performed according to the American Society of Echocardiography Guidelines.[7] A nasal respirometer was used for simultaneous recording of respiration, which was performed by an observer blinded to the other assessments of the protocol. Two-dimensional imaging was performed from parasternal, apical, and subcostal windows. The parasternal, apical views and M-mode recordings were used to detect the presence of respiratory ventricular septal motion. Apical views were also used to detect distortion of ventricular contours caused by constrictive pericardium. The subcostal view was used to identify diameters of the inferior vena cava. Doppler information was obtained from apical, subcostal, right supraclavicular, and parasternal imaging windows. From the apical window, pulsed-wave Doppler recordings at the level of the mitral leaflet tips were used to measure early (E) and atrial (A) diastolic velocities, deceleration time of the E wave, and respiratory variation in the E velocity. Tissue Doppler assessment of mitral annular motion was used to record and compare diastolic early (E) velocities at both the septal and lateral mitral annulus.

Statistical analysis

Descriptive analysis was performed; for quantitative data, central tendency and dispersion measurements are reported as median and interquartile ranges.

Qualitative data was reported as frequencies and percentages. Gal-3 levels were compared between controls and case groups using Wilcoxon rank-sum test, and the chi-square test or Fisher's exact test was used for categorical data. Spearman correlation coefficient was used to analyze the association between Gal-3 levels, parameters of echocardiography, CMR and ergometric test. An alpha error < 5% was considered statistically significant, with a confidence interval of 95%.

Graphics and statistical analyses were performed with Microsoft Excel 2013 and Stata (*version 13.0, Stata Corp., College Station, TX*), with a 2-tailed $p < 0.05$ considered to be significant.

Ethical issues

The institutional review board approved this study that is in compliance with the Declaration of Helsinki. The local ethics committee approved the protocol, and all participants signed a written informed consent.

Results

Baseline characteristics

Twenty-five patients with constrictive pericarditis underwent pericardiectomy.

Median age was 45 years (33-57) with a predominance of men (n = 19, 76%), and median body mass index (BMI) was 25.6 kg/m^2. Comorbidities were hypertension, tobacco use, type 2 diabetes, and chronic arterial disease. All baseline characteristics are listed in Table 1. In the control group, median age was 44 (33-53) years, and 19 were men.

Regarding clinical characteristics, the median length of symptoms before admission was 24 (12-36) months. Median length of hospital and intensive care unit (ICU) stay was eight and two days, respectively. The main clinical signs in the patients were related to right heart failure – jugular vein distention (n = 22, 88%), edema (n = 22, 88%), ascites (n = 18, 72%) – and 16 (64%) had hepatomegaly (n = 16, 64%) at physical examination (Table 1).

Table 1 – Clinical and laboratory measures

Characteristic	Measure
Male sex, n (%)	19 (76)
Age years, median (IQR)	45 (33-57)
BMI, kg/m^2, median (IQR)	25.6 (22-27)
Time of symptoms, months median (IQR)	24 (12-36)
Time of hospitalization, median (IQR)	8 (7-16)
Time of ICU after procedure, median (IQR)	2 (2-3)
Comorbidities, n (%)	
Hypertension	4 (16)
Type 2 diabetes	2 (8)
Chronic arterial disease	3 (12)
Tabagism	5 (20)
Atrial fibrillation	10 (40)
Low voltage ECG	6 (24)
Calcification X-ray	11 (44)
Pleural effusion X-ray	5 (20)
NYHA functional class, n (%)	
I	4 (16)
II	7 (28)
III	11 (44)
IV	3 (12)
Clinical signs, n (%)	
Jugular stasis	22 (88)
Edema	22 (88)
Ascites	18 (72)
Hepatomegaly	16 (64)
Pericardial knock	12 (48)
Kussmaul sign	6 (24)
Paradoxal pulse	5 (20)
Laboratory measurements – median (IQR)	
Galectin-3, ng/mL*	14.8 [9.7-17.2]
Hemoglobin, g/dL,	13.4 [12.8-14.3]
Creatinine, mg/dL,	1.02 [0.99-1.26]
CRP, mg/dL (range)	5.4 [3.2-9.4]
BNP, pg/mL (range)	143 [89-209]

*Continuous variables are presented as median and interquartile range [IQR]. Categorical data are presented as percentage. *risk of postoperative death calculated by EuroSCORE (%). BMI: body mass index; ECG: electrocardiogram; ICU: intensive care unit; NYHA: New York Heart Association; BNP: B-type natriuretic peptide; CRP: C-reactive protein.*

Fourteen (56%) patients presented with New York Heart Association (NYHA) functional class III/IV on admission. Analyzing the clinical signs, patients with ascites had higher Gal-3 levels (16.2 ng/mL [11.6-17.5]) compared with those without ascites, (8.2 ng/mL [6.6-14.8]), with no statistically significant difference though (p = 0.06; CI 95% 0.98-1.72). No association was found of Gal-3 levels with any of the other signs described.

The most frequent etiologic diagnosis was idiopathic (n = 19, 76%), tuberculosis (n = 3, 12%), followed by collagenases (n = 2, 8%), and post-surgery (n = 1, 4%). There were no deaths after pericardiectomy.

Laboratory and complementary tests

The median values of hemoglobin, creatinine, C-reactive protein, BNP and Gal-3 are presented in Table 1. Gal-3 levels were not significantly higher in CCP patients compared with control patients. The median level of Gal-3 was 14.8 [9.7-17.2] ng/mL and 11.8 [10.6-14.2] ng/mL for CCP and controls respectively (p = 0.22). In addition, no significant association was observed between Gal-3 levels and echocardiographic measures (left ventricular diastolic diameter, LVDD; left ventricular systolic diameter, LVSD, left atrial diameter, left ventricular ejection fraction), or with CMR measures (pulmonary artery systolic pressure, PASP > 55 mmHg; left atrial diameter; abnormal septal motion (septal bouncing); vena cava dilatation and myocardial and pericardial late enhancement).

Imaging examinations

All subjects underwent echocardiography and CMR examinations. The median ejection fraction measured by echocardiography and CMR was 60% and 57%, respectively. Analyzing the echocardiographic parameters, only 13 (52%) of the results suggested constrictive pericarditis as a diagnosis. In addition, pericardial thickening was observed in 17 (68%) subjects and inspiratory variation in mitral and tricuspid flow was observed in 13 (52%), suggesting diastolic restriction (Table 2).

The CMR images suggested a CCP diagnosis in 23 (92%) subjects. Pericardial thickness (> 4 mm) was found in 21 (84%) subjects, and the most frequent abnormalities observed were septal bouncing and aortic and vena cava dilatation, both observed in 23 (92%) patients, followed by increased left atrium in 22 (88%) (Table 3).

Cardiopulmonary exercise test

In all subjects, the CPET proved to be safe, without serious complications. The tests were considered effective once median respiratory exchange ratio was 1.1 at both time

Table 2 – Echocardiography and cardiac magnetic resonance variables

Echocardiography variables	N	%
Echo suggests CCP	13	52
Aortic sinus (mm)	30	(29-34)
Left atrium Diastolic diameter (mm)	43.5	(40-47)
Interventricular septum (mm)	8	(8-9)
Posterior wall (mm)	8	(8-9)
RVDD basal (mm)	28	(26-32)
LVDD (mm)	45	(41-46)
LVSD (mm)	29	(27-32)
LVEF (%)	60	(59-66)
Pericardial thickness (> 4 mm)	17	68
Respiratory flow variations (%)	13	52
Cardiac magnetic resonance (CMR)		
CMR suggests CCP	23	92
Pericardial enhancement	6	24
Miocardial enhancement	2	8
Septal bouncing	23	92
Increased Left atrium	22	88
Vena cava dilatation	23	92
LVEF (%)	57	(54-62)
Pericardial thickness (mm)	6	(5-8)
Pericardial thickness (> 4 mm)	21	84

Continuous variables are presented as median and interquartile range [IQR], categorical data are presented as percentage. CCP: chronic constrictive pericarditis; RVDD: right ventricular diastolic diameter; LVDD: left ventricular diastolic diameter; LVSD: left ventricular systolic diameter; LVEF: left ventricular ejection fraction.

points of the study. Overall, after surgical intervention, patients experienced improvement in cardiopulmonary capacity (Table 3) in treadmill speed, peak heart rate, peak oxygen consumption (peak VO_2) at anaerobic threshold (AT), AT, VO_2 and V_E/VCO_2 slope.

BNP values had no correlation with CPET parameters either before or after the pericardiectomy procedure. However, although the Gal-3 marker did not correlate with CPET parameters before the procedure, we observed a moderate inverse correlation with test duration ($r = –0.79$; $p < 0.001$), exercise time ($r = –0.79$; $p < 0.001$), and heart rate at AT ($r = 0.60$; $p = 0.01$) in the postoperative period.

Histopathological study

Histological study was performed of 21 samples. Severe fibrosis and calcification were a common finding, observed in 19 (90.5%) and 12 (57.1%) of the specimens, respectively. Histopathological examination revealed mild inflammation in 16 cases (76.2%). No statistically significant association was found between Gal-3 and these findings (Table 4).

Discussion

Our study showed that patients diagnosed with CCP had normal levels of Gal-3 preoperatively, comparable with the control group. Also, we observed no significant correlation of Gal-3 with echocardiographic and CMR measures and BNP. After pericardiectomy, we observed an improvement in peak VO_2 and V_E/VCO_2 slope, which are makers of poor prognostic. However, we observed negative associations between Gal-3 and CPET parameters after pericardiectomy, such as test duration and exercise time.

Gal-3 has long been known to be a mediator of fibrosis in multiple organs, including the heart, kidney, pancreas, liver, and lung.[8] Nevertheless, no studies have been performed on clinical data of CCP patients, associating levels of Gal-3 with pericardial structure, function, and functional status.

Ntsekhe et al.[5] studied AcSDKP and galectin levels in normal pericardial fluid and tuberculous pericardial effusion.[5] AcSDKP exerts part of its antifibrotic effect by inhibiting Gal-3, which is inactivated by angiotensin-converting enzyme (ACE). The authors concluded that depressed levels of AcSDKP in conjunction with normal or low Gal-3 levels within the pericardium may explain the high incidence of constrictive pericarditis associated with tuberculous pericarditis.

Constrictive pericarditis is a heterogeneous disorder and the risk of constriction after an acute episode is correlated with the etiology. Imazio et al.[9] found a incidence of constrictive pericarditis < 0.5% in idiopathic or viral acute pericarditis; 2.8% for connective tissue disease, 4.0% for neoplastic pericarditis; 20% for tuberculous pericarditis, and 33% for purulent pericarditis. In our cohort, most patients (76%) had an idiopathic etiology, and we cannot extrapolate our results to other etiologies. Only a study with more patients and different etiologies may elucidate whether galectin can modulate constriction.

Inflammation is a physiological process that acts as a trigger for fibrosis and tissue regeneration following injury. The pericardium is a poorly vascularized structure with fibers composed of collagen that generally do not show the delayed enhancement observed with gadolinium injection. In cases where there is hyperemia and inflammation in the pericardium, there is increased vascularization resulting in an increase in late pericardial enhancement on CMR.[10] Zurik et al.[2] also observed that pericardial delayed hyperenhancement on CMR is common in patients with CCP and is associated with histological markers of chronic inflammation and increased neovascularization, which is indicative of an ongoing, dynamic active inflammatory reaction.[2] Patients with CCP without pericardial delayed hyperenhancement had more pericardial fibrosis and calcification and a less pericardial thickening. We also did not observe any significant association of Gal-3 levels with pericardial thickness and pericardial late enhancement evaluated by CMR.

One explanation as to why some patients with CCP do not improve after surgery is myocardial atrophy after prolonged constriction, residual constriction, or a concomitant myocardial process that leads to prolonged cardiac failure in spite of successful pericardiectomy.[11,12] Another possibility is myocardial fibrosis. Probably, the Gal-3-induced fibrosis is restricted to the myocardium and not the pericardium. We also did not

Table 3 – Effect of pericardiectomy on functional capacity

Variables	Pre	Post	p
Velocity (mph)	2.5 [2-2.5]	3 [2.5-3.3]	0.001
Exercise time (min)	9.5 [6.9-11.7]	9.9 [4.5-14]	0.397
Peak HR (bpm)	139 [114-160]	159 [138-178]	0.020
VO_2 at AT (mL/kg/min)	13.5 [11.2-14.6]	16.4 [13.8-20.75]	0.002
AT (%)*	73 [60-81]	69.5 [62.5-78.5]	0.856
peak VO_2 (mL/kg/min)	18.5 [14.6-22.9]	25.4 [22.3-28.6]	< 0.001
peak VO_2 (%)*	63 [49.5-70.5]	82 [69.5-95]	< 0.001
Peak V_E (L/min)	48 [41.3-57.6]	61.7 [44.5-79.9]	< 0.001
V_E/VCO_2 slope RER	35.5 [30-40] 1.1	29 [28-31.5] 1.1	< 0.001 > 0.05

** Percentage in relation to predicted for age and sex. Continuous variables are presented as median and interquartile range [IQR], categorical data are presented as percentage. VO_2: oxygen consumption; AT: anaerobic threshold; HR: heart rate; VO_2: oxygen consumption; VE: pulmonary ventilation; RER: respiratory exchange ratio.*

Table 4 – Histopathologic analysis and galectin-3

	Mild	Severe
Fibrosis		
n (%)	2 (9.5)	19 (90.5)
Gal-3	19.7 [14.2-25.2]	14.8 [9.4-17.2]
Calcification		
n (%)	9 (42.9)	12 (57.1)
Gal-3	16.1 [11.9-20.3]	14.1 [9.5-16.2]
Inflammation		
n (%)	16 (76.2)	5 (23.8)
Gal-3	14.5 [10.5-16.9]	16.1 [9.3-25.2]

Continuous variables are presented as median and interquartile range [IQR], categorical data are presented as percentage. No statistically significant difference was found between the groups.

observe an increase in galectin levels and myocardial delayed enhancement evaluated by CMR and histological analysis.

Cardiopulmonary testing is the most useful tool to objectively assess the exercise capacity of patients with systolic and diastolic heart failure.[6] The test allows assessment of prognosis, efficacy of treatment, and selection for heart transplantation. Moreover, cardiopulmonary testing plays an important role in the prescription of exercises and rehabilitation programs.

Our patients improved peak VO_2 and V_E/VCO_2 slope which are two independent predictors of mortality in heart failure patients with systolic or diastolic dysfunction.[13,14] Also, an increase in peak VO_2 is associated with lower hospital readmissions in heart failure patients, demonstrating the importance of pericardiectomy for these patients.[15]

On the other hand, although numerous studies have evaluated the impact of pericardiectomy on the functional class of patients with CCP, most of them were retrospective case series.[10,12] Moreover, clinical assessment based on NYHA classification is imprecise and subjective. Some patients do not experience recovery in their functional capacity and NYHA functional class.

The associations between Gal-3 levels and exercise intolerance after pericardiectomy suggest the possible role of Gal-3 in the pathophysiology of constrictive pericarditis. This hypothesis should be tested in longer follow-up studies. The finding of Gal-3 as a predictor of improvement in functional capacity is relevant, because it suggests that benefits of pericardiectomy appear to be lower in patients with higher levels of Gal-3.

Conclusion

Gal-3 levels were normal in patients with CCP and did not correlate with morphological and functional measures. The associations between Gal-3 levels and exercise intolerance after pericardiectomy suggest the possible role of Gal-3 in the prognostic prediction after pericardiectomy.

Limitations

The sample consisted of young patients with a predominance of idiopathic etiology in a tertiary cardiology center, which may represent selection bias and limit the external validity of the results. We had only a single time point measure of Gal-3, and therefore we did not assess dynamic changes in this biomarker over time.

Acknowledgment

The authors acknowledge bioMerieux Inc., France, for the Galectin-3 kit donation.

Author contributions

Conception and design of the research AND Analysis and interpretation of the data: Fernandes F, Melo DTP; Acquisition of data: Fernandes F, Melo DTP, Sayegh ALC, Souza FR; Statistical analysis: Sabino EC, Moreira CHV; Obtaining financing: Fernandes F; Writing of the manuscript: Fernandes F, Melo DTP, Ramires FJA, Benvenutti LA, Hotta VT, Sayegh ALC, Souza FR, Dias RR; Critical revision of the manuscript for intellectual content: Fernandes F, Melo DTP, Ramires FJA, Sabino EC, Moreira CHV, Benvenutti LA, Hotta VT, Sayegh ALC, Souza FR, Dias RR, Mady C.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by FAPESP.

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 Hospital das Clínicas da FMUSP under the protocol number 2002.007. 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.

References

1. Adler Y, Charron P, Imazio M, Badano L, Barón-Esquivias G, Bogaert J, et al. 2015 ESC guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015; 36(42):2921–64.
2. Zurick AO, Bolen MA, Kwon DH, Tan CD, Popovic ZB, Rajeswaran J, et al. Pericardial delayed hyperenhancement with CMR imaging in patients with constrictive pericarditis undergoing surgical pericardiectomy: a case series with histopathological correlation. JACC Cardiovasc Imaging. 2011; 4(11):1180–91.
3. Sharma UC, Pokharel S, van Brakel TJ, van Berlo JH, Cleutjens JP, Schroen B, et al. Galectin-3 marks activated macrophages in failure-prone hypertrophied hearts and contributes to cardiac dysfunction. Circulation. 2004; 110(19):3121–38.
4. Filipe MD, Meijers WC, Rogier van der Velde A, de Boer RA. Galectin-3 and heart failure: prognosis, prediction & clinical utility. Clin Chim Acta. 2015 Mar 30; 443:48-56.
5. Ntsekhe M, Matthews K, Wolske J, Badri M, Wilkinson KA, Wilkinson RJ, et al. Scientific letter: Ac-SDKP (N-acetyl-seryl-aspartyl-lysyl-proline) and Galectin-3 levels in tuberculous pericardial effusion: implications for pathogenesis and prevention of pericardial constriction. Heart. 2012; 98(17):1326–8.
6. Balady GJ, Arena R, Sietsema K, Myers J, Coke L, Fletcher GF, et al. American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology; Council on Epidemiology and Prevention; Council on Peripheral Vascular Disease; Interdisciplinary Council on Quality of Care and Outcomes Research. Clinician's Guide to cardiopulmonary exercise testing in adults: a scientific statement from the American Heart Association. Circulation. 2010; 122(2):191–225.
7. Klein AL, Abbara S, Agler DA, Appleton CP, Asher CR, Hoit B, et al. American Society of Echocardiography clinical recommendations for multimodality cardiovascular imaging of patients with pericardial disease: endorsed by the Society for Cardiovascular Magnetic Resonance and Society of Cardiovascular Computed Tomography. J Am Soc Echocardiogr. 2013; 26(9):965–1012.
8. López B, González A, Querejeta R, Zubillaga E, Larman M, Díez J. Galectin-3 and histological, molecular and biochemical aspects of myocardial fibrosis in heart failure of hypertensive origin. Eur J Heart Fail. 2015; 17(4):385–92.
9. Imazio M, Brucato A, Maestroni S, Cumetti D, Belli R, Trinchero R, et al. Risk of constrictive pericarditis after cute pericarditis. Circulation. 2011; 124(11):1270–5.
10. Feng D, Glockner J, Kim K, Martinez M, Syed IS, Araoz P, et al. Cardiac magnetic resonance imaging pericardial late gadolinium enhancement and elevated inflammatory markers can predict the reversibility of constrictive pericarditis after antiinflammatory medical therapy: a pilot study. Circulation. 2011;124(17):1830–7.
11. Bertog SC, Thambidorai SK, Parakh K, Schoenhagen P, Ozduran V, Houghtaling PL, et al. Constrictive pericarditis: etiology and cause-specific survival after pericardiectomy. J Am Coll Cardiol. 2004; 43(8):1445–52.
12. Ling LH, Oh JK, Schaff HV, Danielson GK, Mahoney DW, Seward JB, et al. Constrictive pericarditis in the modern era: evolving clinical spectrum and impact on outcome after pericardiectomy. Circulation. 1999;100(13):1380–6.
13. Piña IL, Apstein CS, Balady GJ, Belardinelli R, Chaitman BR, Duscha BD, et al. American Heart Association Committee on exercise, rehabilitation, and prevention Exercise and heart failure: A statement from the American Heart Association Committee on exercise, rehabilitation, and prevention. Circulation. 2003; 107(8):1210-25.
14. Salemi VM, Leite JJ, Picard MH, Oliveira LM, Reis SF, Pena JL, et al. Echocardiographic predictors of functional capacity in endomyocardial fibrosis patients. Eur J Echocardiogr. 2009; 10(3):400-5.
15. Piña IL, Bittner V, Clare RM, Swank A, Kao A, Safford R, et al. HF-ACTION Investigators. Effects of exercise training on outcomes in women with heart failure: analysis of HF-ACTION (Heart Failure-A Controlled Trial Investigating Outcomes of Exercise TraiNing) by sex. JACC Heart Fail. 2014; 2(2):180-6.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Galectin-3 in Chronic Constrictive Pericarditis: Accurate Information for the Good Doctor

Wolney de Andrade Martins[1,2]

Universidade Federal Fluminense, Departamento de Medicina Clínica,[1] *Niterói, RJ – Brazil*

Complexo Hospitalar de Niterói,[2] *Niterói, RJ – Brazil*

Short Editorial related to the article: Galectin-3 Levels in Patients with Chronic Constrictive Pericarditis

Galectin-3 (Gal-3), which is now known as a new biomarker, has traveled the rigorous scientific pathway from discovery to validation. Experimental and clinical studies described its elevation in several situations, such as tumors, renal failure and heart failure.[1] Its administration caused myocardial fibrosis and heart failure (HF). Its genetic suppression or inhibition prevented fibrosis and remodeling, that is, the cause-and-effect relationship had been proven.[2] Elevated levels of Gal-3 show a worse prognosis, as they predict sudden death. Galectin-3 was an independent predictor in the short and medium term of hospitalizations and of mortality in patients with HF, especially those with heart failure with preserved ejection fraction (HFpEF).[3]

The biomarker can assist the clinician in their diagnostic dilemmas, in assessing the prognosis and even guiding the therapy. The HFpEF is an example of condition where all help is welcome. Multiple comorbidities, less typical conditions, especially in the elderly and obese, can be confusing. HFpEF is one of the situations where Gal-3 can greatly assist in diagnostic confirmation.[4]

Fernandes et al.[5] present a case-control study in which they compared 33 patients with chronic constrictive pericarditis (CCP), predominantly idiopathic, with healthy volunteers. The rationale was that the fibrosis present in the CCP raised the levels of Gal-3, and this was related to the morphological and functional changes typical of CCP. There was confirmation of the diagnosis of CCP by imaging methods, echocardiography and cardiac resonance, as well as surgical ones. It was a difficult study to carry out and only possible in a reference center. The results were negative and there is a plethora of possible explanations. A selective sample of patients with idiopathic CCP is indicated by the authors. We know that tuberculous pericarditis, which is of paramount importance in areas where tuberculosis is endemic, has a more severe clinical course, with a common evolution to fibrosis and constriction. Gal-3 itself has limitations due to its non-specificity. It is found in inflammatory and fibrotic processes in the lungs, kidneys, liver, pancreas, and in cancer patients, among others.

Historically, we sought to attain the differential diagnosis between constrictive pericarditis and restrictive cardiomyopathies through clinical and laboratory parameters. It is plausible to assume that Gal-3 should be higher in the second clinical situation, due to the magnitude of myocardial and interstitial involvement. Theoretically, Gal-3 could also provide us with how much the clinical picture is due to myocardial dysfunction in cardiomyopathies or diastolic restriction in constrictive pericarditis. That is, there are still countless questions without answers based on evidence.[6]

Considering a patient with a clinical picture of right ventricular failure or during the investigation of ascites and "normal" Gal-3 values, the publication by Fernandes et al.[5] allows us to infer points in favor of the diagnosis of CCP to the detriment of restrictive cardiomyopathies or other diseases.

The study of Fernandes et al.[5] brought us the novelty of Gal-3 measurement in a very specific situation such as the CCP. It clearly showed that there was no significant increase in Gal-3 or an association with morphological or functional parameters. The quality of the research of Fernandes et al., herein published in Arq Bras Cardiol., lies not only on its originality, but also on its methodological criteria and rigor regarding its conclusions. The present study raises new questions. Would there be a difference between the CCP etiologies? Would there be any applicability of Gal-3 in differentiation with restrictive cardiomyopathies? What about the usefulness of serial measurements of Gal-3?

To paraphrase Dr. Alan Maisel, a renowned resercher of biomarkers in cardiology, "the biomarker will make the bad doctor worse and the good doctor better".[7] Therefore, the information now incorporated into the literature by the authors will be very useful to us, provided it is used within a critical clinical sense.

Keywords

Galectin-3; Biomarkers; Pericarditis Constrictive; Cardiomyopathy, Restrictive; Pericardium; Inflammation; Cardiomyopathy, Restrictive.

Mailing Address: Wolney de Andrade Martins •
Universidade Federal Fluminense, Departamento de Medicina Clínica – Rua Marques do Paraná, 303, 6º andar. Postal Code 24030215, Centro, Niterói, RJ – Brazil
E-mail: wolney_martins@hotmail.com

DOI: https://doi.org/10.36660/abc.20200163

Short Editorial

References

1. de Boer RA, Voors AA, Muntendam P, van Gilst WH, Veldhuisen DJ. Galectin-3: a novel mediator of heart failure development and progression. Eur J Heart Fail. 2009;11(9):811-7.
2. de Boer RA, Daniels LB, Maisel AS, Januzzi Jr JL. State of the art: newer biomarkers in heart failure. Eur J Heart Fail. 2015;17(6):559-69.
3. Meijers WC, Januzzi JL, de Filippi C, Adourian AS, Shah SJ, van Veldhuisen DJ, de Boer RA. Elevated plasma galectin-3 is associated with near-term rehospitalization in heart failure: a pooled analysis of 3 clinical trials. Am Heart J. 2014;167(6):853-60.
4. de Boer RA, Edelmann F, Cohen-Solal A, Mamas MA, Maisel A, Pieske B. Galectin-3 in heart failure with preserved ejection fraction. Eur J Heart Fail. 2013;15(10):1095-101.
5. Fernandes F, de Melo DTP, Ramires FJA, Sabino EC, Moreira CHV, Benvenutti LA, et al. Galectina-3 em pacientes com pericardite constrictiva crônica. Arq Bras Cardiol. 2020; 114(4):683-689.
6. Fadl SA, Nasrullah A, Harris A, Edwards R, Kicska G. Comprehensive review of pericardial diseases using different imaging modalities. *Int J Cardiovasc Imaging*. (2020). https://doi.org/10.1007/s10554-020-01784-x
7. Maisel AS (ed.) Biomarkers for clinicians. Expert advice for clinicians. New Delhi: Jaypaee Brothers Medical Publishers Ltd; 2012.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Role of Interleukin-18 and the Thrombus Precursor Protein in Coronary Artery Disease

Carlos Scherr,[1,2,5] Denilson Campos de Albuquerque,[2] Roberto Pozzan,[3] Kezia Ataide,[4] Talita Ludmila,[5] Fernanda Blanco,[5] Claudio Martins Mangia[5]

Ministério da Saúde – Cardiologia,[1] Brasília, DF - Brazil
Universidade do Estado do Rio de Janeiro – Cardiologia,[2] Rio de Janeiro, RJ - Brazil
Universidade do Estado do Rio de Janeiro – Cardiologia/Hipertensão,[3] Rio de Janeiro, RJ - Brazil
Hospital Universitário Pedro Ernesto – Cardiologia,[4] Rio de Janeiro, RJ - Brazil
Fundação Pró Coração – Cardiologia,[5] Rio de Janeiro, RJ – Brazil

Abstract

Background: **Coronary failure is the leading cause of death worldwide and identifying patients at higher risk for coronary artery disease (CAD) is a challenge.**

Objectives: **To test the biomarkers interleukin 18 (IL-18) and thrombus precursor protein (TpP), involved in atherogenesis, to aid in the early assessment of CAD.**

Methods: **This was a cross-sectional cohort of 119 patients, stratified into three groups: Group I - acute coronary syndrome (39); Group II - chronic CAD (40) and Group III - control, without coronary lesion, but who might have risk factors for CAD (40). Statistical analysis was performed using the statistical program SPSS (Statistical Package for the Social Sciences) for Windows ,version 17.0 of 2008. The significance level was set at 0.05 or 5% ($p < 0.05$), with a 95% confidence interval. Chi-square test ($\chi 2$), Analysis of variance (ANOVA), and Tukey's test were used.**

Results: **The mean age was 60.36 ± 9.64 years; there was a prevalence of females in Group III (65.0% $p = 0.002$), but without statistical significance for the means of IL-18 and TpP. The means of IL-18 and TpP were increased in Group I when compared to the other groups; IL-18 = 1325.44 ± 1860.13 ng/dL, $p = 0.002$; TpP = 35.86 ± 28.36 μg / mL, $p < 0.001$). When compared two-by-two, it was observed that Group I had higher mean IL-18 and TpP values than Group II (IL-18 = 353.81 ± 273.65 ng / dL; TpP = 25.66 ± 12, 17 μg / mL) and Group III (IL-18 = 633.25 ± 993.93 ng / dL; TpP = 18.00 ± 8.45 μg / mL).**

Conclusion: **There was an increase in these biomarkers in acute CAD, suggesting a relationship with the atherosclerotic plaque instability process, but not with the chronic phase. (Arq Bras Cardiol. 2020; 114(4):692-698)**

Keywords: **Cardiovascular Diseases/mortality; Coronary Artery Diseases; Interleukin 18; Biomarkers; Acute Coronary Syndrome/prevention and control**

Introduction

Coronary artery disease is one of the main manifestations of cardiovascular disease in the 21st century, and its importance lies in its high morbidity and mortality. The identification of patients at higher risk becomes necessary to contribute to the improvement of this condition and rationalize costs.[1] Modern medicine has developed rapidly in the field of prevention, early detection and screening of diseases, not being restricted to treatment.

Therefore, early detection associated with the immediate treatment of cardiovascular disease (CVD) has become one of the most challenging tasks for doctors and researchers worldwide. Several biomarkers have been studied in recent years in the diagnosis, prognosis, prediction of adverse events and therapeutic monitoring.[2] However, the first initiative towards prevention is to apply strategies to identify the individual likely to have atherosclerotic events. In this sense, in addition to the widely known risk factors contributing to the process of identifying vulnerable individuals, the use of biomarkers involved in atherogenesis can be a key factor in the risk assessment of coronary artery disease (CAD).[3,4]

Atherosclerosis is a chronic, multifactorial, slow and progressive inflammatory disease, resulting from several specific cell and molecular responses that lead to endothelial aggression, affecting mainly the intima layer of medium and large-caliber arteries.

Generally, the rupture of the fibrous capsule of the atherosclerotic plaque leads to thrombosis, which to a lesser extent can result from superficial endothelial erosion. Ruptured plaques are usually associated with inflammation

Mailing Address: Carlos Scherr •
Ministério da Saúde – Cardiologia - Rua Visconde de Pirajá, 595 / 1204. Postal Code 22410-003, Ipanema, RJ – Brazil
E-mail: carlos.scherr@all.com.br
Manuscript received March 14, 2019, revised mansucript June 11, 2019, accepted June 23, 2019

DOI: https://doi.org/10.36660/abc.20190176

of the intima and adventitia, intra-plaque hemorrhage, exposure of thrombogenic material to the bloodstream, triggering platelet accumulation, coagulation cascade activation and fibrin deposition.[5]

The inflammatory response in atherogenesis consists of functional alterations in endothelial cells, T-lymphocytes, monocyte-derived macrophages, smooth muscle cells and, in the early stages, it is caused by the accumulation of lipids in the arterial walls.[6] The activation of these cells triggers the formation and interaction of several cytokines, adhesion molecules, growth factors, accumulation of lipids and proliferation of smooth muscle cells. In addition to these factors, the inflammatory response can be induced by oxidative stress (oxidation of low-density lipoprotein - LDL).[7,8]

Currently, new biomarkers are being studied in association with acute or chronic coronary syndrome and correlated with the prognostic value, which is the objective of this study.

Two of them were evaluated in this study: the thrombus precursor protein (TpP) and interleukin 18 (IL-18) in individuals with acute myocardial infarction with and without ST-elevation, unstable angina (UA), chronic coronary artery disease and individuals who had no evidence of obstructive coronary atherosclerotic disease, but in the presence of risk factors for CAD. The choice of biomarkers was based on their involvement with the inflammatory (IL-18) and thrombotic (TpP) processes, within the context of atherosclerosis and aggravation of atherosclerotic disease.

TpP is a biomarker used to estimate soluble fibrin polymers. Elevated levels of TpP indicate a pro-thrombotic status and active thrombogenesis. In patients with ACS, increased levels of this biomarker are associated with a higher risk of death and ischemic complications; therefore, TpP has been shown to be an independent marker for adverse cardiovascular outcomes.[9] The IL-18 biomarker is a pro-inflammatory cytokine, closely associated with atherosclerotic plaque instability, and is therefore a good predictor of undesirable events in ACS.[10,11] In an observational study, it was also shown to be a good predictor of adverse cardiovascular events in chronic coronary disease over two years.[12]

Studying patients vulnerable to atherosclerotic disease and even being able to have severity parameters in those with the disease already present through new markers has been a challenge for current medical research. In this context, the new biomarkers occupy an important space, considering the morbidity and mortality aspect of coronary disease, which may become predictors of cardiovascular events and thus contribute to the prevention, early detection and screening of CAD.

Methods

Primary endpoint

To evaluate the serum levels of biomarkers: interleukin 18 (IL-18) and thrombus precursor protein (TpP) in patients with acute or chronic coronary syndrome in relation to the control group.

Secondary endpoints

To verify the association of serum levels of biomarkers interleukin 18 (IL-18) and thrombus precursor protein (TpP) with disease chronicity, worsening of coronary artery disease or absence of obstructive coronary atherosclerotic process. To evaluate the association between epidemiological, anthropometric data and risk factors of the studied population with the biomarkers interleukin 18 (IL-18) and thrombus precursor protein (TpP).

In this cross-sectional cohort, 119 patients, of both genders, older than 30 years of age, were stratified into three groups: acute (Group I - n = 39), chronic (Group II - n = 40) and control (Group III - n = 40), according to the inclusion and exclusion criteria established for the study and compared with the quantitative analysis of two biomarkers: IL-18 and TpP.

Patients belonging to Group I (acute) were recruited based on the typical clinical history of acute coronary syndrome (NSTEMI, STEMI, and UA), plus electrocardiographic data and cardiac enzymes at admission. Once identified, blood was collected within 48 hours of symptom onset, for subsequent biomarker measurement. The selection was made sequentially, according to the inclusion criteria, as these patients were admitted to the hospital. Patients belonging to Group II were selected sequentially based on the clinical history of chronic CAD confirmed by some imaging method (cardiac catheterization - CAT or coronary angiotomography - Angio-CT) or clinical report of previous AMI (with complementary exams demonstrating the condition - electrocardiogram - ECG and myocardial markers). Group III (control) consisted of patients who had risk factors for CAD in the absence of obstructive coronary lesion at the time of admission to the database. The absence of atherosclerotic obstructive coronary lesion was ruled out through cardiac catheterization or coronary angiotomography.

Inclusion criteria

• **Group I (acute) -** ACS (NSTEMI, STEMI and UA) a) AMI with or without ST-elevation demonstrated by the positive curve of myocardial necrosis markers (troponin), associated with ECG. b) UA based on the classically described clinical picture and complementary exams (electrocardiogram - ECG and cardiac catheterization - CAT). c) Measurement of biomarkers performed within the first 48 hours of symptom onset.

• **Group II (chronic) -** chronic CAD a) confirmation by imaging method (cardiac catheterization or coronary angiotomography) or with a clinical history of previous coronary disease - previous AMI (diagnosis over six months before, confirmed by ECG and necrosis markers).

• **Group III (control)** a) Presence or not of one or more risk factors for CAD: SAH, dyslipidemia (DLP), diabetes mellitus (DM), physical inactivity, smoking, ex-smoker, chronic renal failure, obesity. b) Cardiac imaging examination that proved the absence of obstructive coronary lesion: CAT or angio-CT, performed in the last six months prior to admission to the database.

The following exclusion criteria were adopted:

Group I (acute): a) coronary artery bypass grafting surgery performed less than six months before. b) Chronic renal failure undergoing dialysis or clearance <30 mL / min. c) Terminal illnesses. d) Ejection fraction prior to ACS <40% (Simpson); e) Not signing the Free and Informed Consent (FIC) form.

Group II (chronic): the same as group I plus, a) decompensated DM. b) AMI that occurred less than six months before. c) Unstable angina. d) Class IV stable angina according to the Canadian Cardiovascular Society. d) Functional class III and IV according to the New York Heart Association (NYHA).

Group III (control): a) presence of any obstructive coronary lesion, even if incipient. b) Chronic renal failure undergoing dialysis or clearance <30 mL / min. c) Terminal illnesses. d) Ejection fraction <40% (using the Simpson method). e) Stable angina. f) Unstable angina. g) AMI. h) Decompensated DM. i) NYHA functional class III and IV. j) Not signing the FIC form.

Storage and laboratory methods

For the measurement of TpP, 4 mL of venous blood were collected, placed in a tube with sodium citrate and centrifuged. After centrifugation, two 1-mL aliquots of plasma were removed to be frozen at -80 °C. The analysis was carried out later using the ELISA method. For the measurement of IL-18, 8 mL of venous blood were collected and placed in a serum gel tube. After collection, we waited 30 min for clot retraction and subsequent centrifugation. After centrifugation, two 1-mL aliquots of serum were removed to be frozen at -80 °C. The analysis was also performed later using the ELISA method.

Statistical analysis

The data obtained were analyzed using the statistical program SPSS (Statistical Package for the Social Sciences for Windows), version 17.0 of 2008. The level of significance was set at 0.05 or 5% ($p < 0.05$) and the confidence interval at 95%. The following statistical methods were used: Analysis of variance (One-way ANOVA F): used to compare the means of variables that showed normal distribution and had homogeneity of variances by the Levene test. Tukey's test: used as a complement to the analysis of variance, to compare the means of variables 2 by 2. Chi-square test (χ^2): used to compare the frequency distributions of the categorical variables from independent samples. This study sample size was determined by a convenience sample; however, it followed the order of recruitment, that is, the first 39 patients in the acute phase of the two participating institutions, the first 40 chronic patients and the 40 controls.

This study was approved by the Ethical Committees of HUPE and INC, where patients were recruited, under numbers 2667/2010 CAAE: 0115.0.228.000-10 and 141.432/2012 CAAE: 09086412.9.1001.5272, respectively. The participants signed the Free and Informed Consent (FIC) form before any procedure related to the study was performed.

Results

The mean age was 59.5 ± 9.7 years (range: 35-83 years), with no statistically significant difference between the groups. In groups I and II there was a predominance of males and in Group III, of females ($p = 0.002$).

Regarding the risk factors of the overall sample, it is noteworthy the high incidence of sedentary lifestyle, overweight / obesity and arterial hypertension in all groups.

Table 1 shows the risk factors for CAD between the studied groups. It was observed that only dyslipidemia, being an ex-smoker and physical inactivity showed a statistically significant difference. Group II had a higher prevalence of dyslipidemic individuals when compared to the other groups; Group III had a higher prevalence of non-smoking individuals than the other groups; and Group I had a higher prevalence of sedentary individuals compared to the others. There was no association between risk factors, ethnicity or gender with the results obtained of the markers in all analyzed groups.

Mean of intergroup and intragroup IL-18 and TpP markers in table 2

Regarding the differences in the means of IL-18 levels between the groups, it was observed that Group I had higher values than the other groups (1325.44 ± 1860.13 pg / mL), with statistical significance. In the two-by-two comparison, Group I had a higher mean than Groups II (353.81 ± 273.65 pg / mL) and III (633.25 ± 993.93 pg / mL), but Groups II and III showed statistically equal means. Those with instability of atherosclerotic disease had higher levels of IL-18 when compared to patients who had stable coronary lesion or those who had risk factors for CAD in the absence of a coronary atherosclerotic process, allowing us to infer that the increase in IL-18 levels is associated with atherosclerotic plaque instability.

Regarding the TpP biomarker between the groups, higher values were observed in Group I (35.86 ± 28.36 μg / mL), respectively, $p < 0.001$) when compared with the other groups. In the two-by-two comparison, Group I also had a higher mean than Groups II (25.66 ± 12.17 μg / mL) and III (18.0 ± 8.45 μg / mL); however, when Groups II and III were compared, it was observed that the means were statistically equal (Table 2).

Discussion

The identification of asymptomatic individuals with atherosclerosis is essential to implement secondary treatment and prevention measures, as well as those with a possibly more unfavorable evolution.

Mallat et al.[13] showed that plasma concentrations of IL-18 are increased in patients with ACS with or without myocardial necrosis, also pointing out that the concentrations correlate with the myocardial dysfunction severity. They studied a sample of 53 patients, admitted to a cardio-intensive unit with chest pain and alteration of the ST-segment in a sequential manner; after troponin analysis, they were selected for the UA or AMI group. The patients belonging to the UA group had a mean IL-18 level

Table 1 – Risk factors for CAD in the study groups

Risk factors	Group I		Group II		Group III		Statistic test	p
	n	%	n	%	n	%		
SAH								
Yes	31	79.5	28	70.0	32	80.0	χ^2=1.4	0.495
No	8	20.5	12	30.0	8	20.0		
DLP								
Yes	16	41.0	32	80.0	18	45.5	χ^2=14.8	0.001
No	23	59.0	8	20.0	22	55.0		
DM								
Yes	12	30.8	10	25.0	8	20.0	χ^2=1.2	0.544
No	27	69.2	30	75.0	32	80.0		
SMOKER								
Yes	3	7.7	5	12.5	0	0.0	χ^2=5	0.079
No	36	92.3	35	87.5	40	100.0		
EX-SMOKER								
Yes	15	38.5	22	55.0	7	17.5	χ^2=12.1	0.002
No	24	61.5	18	45.0	33	82.5		
SEDENT								
Yes	38	97.4	31	77.5	31	77.5	χ^2=7.7	0.021
No	1	2.6	9	22.5	13	22.5		
OVER/OBES								
Yes	30	76.9	31	77.5	27	67.5	χ^2=1.3	0.521
No	9	23.1	9	22.5	13	32.5		
CRF								
Yes	2	5.1	2	5.0	0	0.0	χ^2=2.0	0.351
No	37	94.9	38	95.0	40	100.0		

Grupo I: pacientes agudos (SCA); Grupo II: pacientes crônicos (DAC); Grupo III: grupo-controle (com Risk factors para DAC, mas sem lesão coronariana); DAC: doença arterial coronariana; HAS: hipertensão arterial sistêmica; DLP: dislipidemia; DM: diabetes melito; TAB: tabagismo; Ex-TAB: ex-tabagismo; SEDENT: sedentarismo; SOB/OBES: sobrepeso/obesidade; IRC: insuficiência renal crônica. Corrigido pelo teste exato de Fisher.

Table 2 – Means of the IL-18 and TpP biomarkers of the study groups

Biomarkers	Group I	Group II	Group III	Statistic test	p	Comp. 2 by 2
IL-18 (pg/ml)	1325.44	353.81	633.25	F=6.61	0.002	GI>GII
	(±1860.13)	(±273.65)	(±993.93)			GII=GIII
						GI>GIII
TpT (µg/mL)	35.86±28.36	25.66±12.17	18.0±8.45	F=9.31	0.000	GI>GII
						GII=GIII
						GI>GIII

of 214.7 (116.6-297.0) pg / mL, and those belonging to the AMI group had a mean of 164.6 (53.6-602.5) pg / mL. These patients were compared to two more groups: one with stable coronary artery disease (n = 9) and another group (n = 11) without coronary lesions (control group). It was observed that the mean IL-18 levels in the control group (46.8 (34.2-68.2) pg / mL) were significantly different from those with stable angina (85.7 (56.0- 157.7) pg / mL, p <0.01), suggesting that IL-18 concentrations in patients with stable coronary artery disease may be associated with the presence of advanced coronary artery disease. In the group of patients with unstable angina, the mean IL-18 levels were significantly higher than in the control group (p <0.001) or in the group with stable angina (p = 0.001). In the group of patients with AMI, the mean IL-18 levels were also significantly higher than in the control group (p <0.001) or the group with stable angina (p <0.01). IL-18 levels did not significantly differ between the group with unstable angina and the group with AMI.[13] In this same study, it was observed that serum IL-18 levels were significantly correlated with myocardial dysfunction severity, assessed by determining the ventricular ejection fraction (EF); the mean EF between the groups was 55% and mean IL-18 values were 46.8 pg / mL for non-coronary patients, 85.7 pg / mL for patients with stable angina, 214 pg / mL for those with unstable angina and 164.6 pg / mL for patients with acute myocardial infarction. Comparing with the results found in this study, it was observed that the mean EF between the groups was 65.09% and the mean levels of IL-18 were higher in Group I when compared to Group II and Group III; however, in this population (n = 119), systolic function distribution within normality was obtained for all groups, and Group I showed a slight reduction in the prevalence of individuals with normal EF, without statistical significance. It was also observed that the levels of IL-18 in patients with chronic CAD and without coronary lesions were statistically equivalent, not replicating the previous results.

Blankenberg et al.[14] showed in their prospective study carried out with a cohort of 1229 patients with documented coronary heart disease and followed for an average of 3.9 years, that 95 patients died from cardiovascular causes and the mean IL-18 serum concentrations were significantly higher in patients with a fatal cardiovascular event than the ones without it (68.4 pg / mL vs. 58.7 pg / mL, p <0.001). This study included patients with stable angina (n = 855) and patients with unstable angina (n = 373) and the predictive value of IL-18 in relation to cardiovascular death was evaluated. It was observed that both groups showed an evident increase in the risk of fatal cardiovascular events according to the mean value of IL-18; however, the group of patients with unstable angina showed a higher value of this marker. The authors draw attention to this last analysis, since the group with unstable angina had a smaller sample size than the group of patients with stable angina; thus, the serum level of IL-18 can be identified as a strong independent predictor of death from cardiovascular causes in patients with CAD, regardless of the clinical status at admission. This result strongly supports the experimental evidence of IL-18-mediated inflammation, allowing the acceleration and vulnerability of atherosclerosis.[14]

Studies have shown that the increase in serum IL-18 levels is also associated with some risk factors, such as type 2 DM and metabolic syndrome, in addition to the atherosclerosis severity.[15]

Suchanek et al.[16] analyzed the increase in serum IL-18 levels in patients with CAD and type 2 DM. The authors evaluated a group of 130 patients with advanced CAD (at least two coronary lesions, one with stenosis >70%), and 43 were selected, with a previous diagnosis of DM undergoing treatment and another group with 31 healthy patients (control group). The groups were similarly matched for age, BMI, DLP, smoking; a higher level of IL-18 was observed in patients with CAD (463.48 ± 111.7 pg / mL) when compared to the control group (248.99 ± 103.69 pg / mL), but patients with CAD and DM showed a higher level of IL-18 when compared to CAD patients without DM (500 pg / mL vs. 430 pg / mL, p = 0.04). The mechanisms responsible for the increase in IL-18 levels in diabetic patients are yet to be fully clarified; however, it is believed that deficient glycemic control, diabetic nephropathy, obesity and inflammation are considered possible causes to justify the increase in serum IL-18 levels in this patient profile.[16] In the present study, there was no statistically significant difference when the risk factor DM was compared between the groups of patients associated with the serum level of IL-18, showing that samples from patients with ACS, chronic CAD and healthy patients were similar to each other.

In an observational study similar to this, albeit with a prospective analysis, 194 patients, 75 of which were acute and 119 chronic, were compared with 68 controls. The analysis of smooth muscle cells from the aorta showed higher values in patients with coronary disease than in controls and that IL-18 may be an independent risk factor for CAD. [17]

In another study with 118 patients with coronary disease undergoing an angiographic study, consisting of 67 in the acute phase and 51 with stable angina, the levels of IL-18 were significantly higher in the acute ones compared to the chronic ones, which is in accordance with the results presented herein.[18]

Regarding thrombus formation, Goetze emphasizes the importance of the increase in TpP levels in patients with CAD, highlighting the relevance of having an active thrombosis marker to provide important information in the ongoing ACS.[19]

Following the same concept, Mega et al.[20] emphasized the prognostic value of TpP in patients with ACS, showing that increased TpP levels are associated with a higher risk of death and ischemic complications, making it clear that the inclusion of an activated coagulation marker, such as TpP, in patients with established cardiovascular disease and risk factors for CAD can offer a valuable complementary analysis in the risk assessment of ACS. Carried out with 284 healthy patients and 2349 patients with ACS, this study found that the mean level of TpP was higher in patients with ACS (8.9 μg / mL vs. 3.6 μg / mL, p <0.001), which is correlated a worse prognosis.[20] In the present study, it

was observed that TpP levels were significantly higher in patients diagnosed with ACS than in patients with chronic CAD and in the control group (p <0.001). However, as this is an observational study, there was no prognostic evaluation of these patients, preventing a better analysis of the clinical outcomes that could be correlated; however, the evaluation of these data is planned.

Laurino et al.[21] studied a cohort of 115 patients with symptoms suggestive of AMI with less than six hours duration of pain onset. Blood samples from patients were measured at 0, 1, 2, 4, 8, 16 and 24 hours after presentation for some biomarkers: total creatine kinase (total CK), CK-MB, myoglobin, troponin I and TpP. The authors observed a significant increase in serum TpP levels in 15 of the 17 patients with AMI diagnosed within six hours after symptom onset (p <0.001); 2 of the 8 patients who had AMI diagnosed six hours after symptom onset (p <0.008); 22 of the 35 patients with unstable angina (p <0.001) and 15 of the 30 patients with stable angina (p <0.001) and 3 of the 5 patients with atrial fibrillation (p <0.001); 6 of 9 patients with congestive heart failure (p <0.001); and 6 of 11 patients with non-cardiac chest pain (p <0.001). Maximum TpP concentrations in patients with AMI preceded those of the other markers by two to four hours.[21] Therefore, acute thrombosis is associated with significant clinical alterations, including AMI. An accurate, fast and reliable test for the detection of thrombus would be an invaluable tool for doctors in the diagnosis, monitoring and treatment of patients with acute chest pain.[22]

Studies have demonstrated the importance of TpP in the assessment of the acute thrombotic process, highlighting the ACS, while others associate the increased values of this biomarker to the presence of some risk factors for CAD, such as SAH and DM in patients without evidence of ACS. As these risk factors favor a state of hypercoagulability, they may be related to a pro-thrombotic effect and may trigger an active thrombogenic process. The presence of type 2 DM may be associated with increased serum TpP values due to the predisposition of this patient profile to have markedly increased endothelial dysfunction, in addition to greater systemic coagulation activation, which caused transient alterations and favors acute cardiac events.[22,23,24] The presence of SAH can also result in a hypercoagulable and prothrombotic environment and favor acute decompensation of coronary artery disease.[23,24] The present study showed that DM and SAH did not result in a statistically significant difference between the studied groups, having not influenced the final result of the TpP measurement in relation to the different stages of coronary disease (presence of risk factor, chronic CAD and ACS). Therefore, the result obtained was not influenced by these risk factors.

Study limitations

The sample size is small, representing a convenience sample, which can be attributed to two factors: the selection of patients carried out in hospitals that did not have an open emergency unit, making it difficult to constitute the group of acute patients. The analysis of the means found for IL-18 and TpP showed an equality between the group of chronic patients and the control group. Making a critical assessment of this observation, it can be noted that no complementary exams (e.g., carotid and vertebral Doppler) or intravascular ultrasound were performed to rule out an atherosclerotic process in other sites, which may have influenced this result, not allowing a better evaluation of biomarkers with chronicity or absence of atherosclerosis. A normal ejection fraction in all groups excluded more severe patients, which may have influenced the results. Although the present study showed that the mean serum levels of IL-18 and TpT were higher in the group of acute patients when compared to the group with stable angina or the one without coronary lesions, it is not possible to make a prognostic evaluation, as it aims to encourage the continuity of the research to confirm the hypothesis and intends to do an annual monitoring of the subjects in this sample.

Conclusions

The mean IL-18 and TpP levels are elevated in the acute phase of coronary artery disease, suggesting the correlation of this biomarker with the worsening and the instability of acute coronary syndrome.

The mean levels of IL18 and TpP were lower in the chronic phase of coronary disease and in the patients of the Control Group; however, in this study it was observed that the Chronic Group and the Control Group had statistically equivalent means.

The results were not influenced by differences in gender or ethnicity in the groups.

Author contributions

Conception and design of the research and Critical revision of the manuscript for intellectual content: Scherr C, Albuquerque DC; Acquisition of data: Scherr C, Ataide K, Ludmila T, Blanco F, Mangia CM; Analysis and interpretation of the data and Writing of the manuscript: Scherr C, Albuquerque DC, Ataide K; Statistical analysis: Scherr C, Albuquerque DC, Pozzan R; Obtaining financing: Scherr C, Albuquerque DC, Ludmila T.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by Fundação Pró Coração.

Study Association

This article is part of the thesis of Doctoral submitted by Carlos Scherr, from Universidade do Estado do Rio de Janeiro.

References

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics – 2013 update: a report from the American Heart Association. Circulation. 2013;127(1):e6-245.
2. Bouras G, Deftereos S. Editorial (hot topic: cardiovascular disease biomarkers: from tradition to modernity). Curr Top Med Chem. 2013;13(2):79-81.
3. Vasan RS. Biomarkers of cardiovascular disease: molecular basis and practical considerations. Circulation. 2006;113(19):2335-62.
4. Hackam DG, Anand SS. Emerging risk factors for atherosclerotic vascular disease: a critical review of the evidence. JAMA. 2003;290(7):932-40.
5. Shah PK. Biomarkers of plaque instability. Curr Cardiol Rep. 2014;16(12):547.
6. Nicolletti A, Caligiuri G, Hansson GK. Immunomodulation of atherosclerosis: myth and reality. J Intern Med. 2000;247(3):397-405.
7. Kunsch C, Medford RM. Oxidative stress as a regulator of gene expression in the vasculature. Circ Res.1999;85(8):753-66.
8. Abela OG, Ahsan CH, Alreefi F, Salehi N, Baig I, Janoudi A, et al. Erratum to: plaque rupture and thrombosis: the value of the atherosclerotic rabbit model in defining the mechanism. Curr Atheroscler Rep. 2016;18(8):52.
9. Mega JL, Morrow DA, Lemos JA, Mohanavelu S, Cannon CP, Sabatine MS. Thrombus precursor protein and clinical outcomes in patients with acute coronary syndromes. J Am Coll Cardiol. 2008;51(25):2422-9.
10. Hartford M, Wiklund O, Hultén LM, Persson A, Karlsson T, Herlitz J, et al. Interleukin-18 as a predictor of future events in patients with acute coronary syndromes. Arterioscler Thromb Vasc Biol. 2010;30(10):2039-46.
11. Balta S, Demirkol S, Kucuk U, Unlu M, Ay SA, Arslan Z, et al. Inflammatory markers may predict long-term cardiovascular mortality in patients with acute coronary syndrome. Cardiology. 2013;125(2):88-9.
12. Opstad TB, Arnesen H, Pettersen AÅ, Seljeflot I. Combined elevated levels of the proinflammatory cytokines IL-18 and IL-12 are associated with clinical events in patients with coronary artery disease: an observational study. Metab Syndr Relat Disord. 2016;14(5):242-8.
13. Mallat Z, Henry P, Fressonnet R, Alouani S, Scoazec A, Beaufils P, et al. Increased plasma concentrations of interleukin-18 in acute coronary syndromes. Heart. 2002;88(5):467-9.
14. Blankenberg S, Tiret L, Bickel C, Peetz D, Cambien F, Meyer J, et al. Interleukin-18 is a strong predictor of cardiovascular death in stable and unstable angina. Circulation. 2002;106(1):24-30.
15. Opstad TB, Pettersen AA, Arnesen H, Seljeflot I. Circulating levels of IL-18 are significantly influenced by the IL-18 +183 A/G polymorphism in coronary artery disease patients with diabetes type 2 and the metabolic syndrome: an observational study. Cardiovasc Diabetol. 2011 Dec 5;10:110.
16. Suchanek H, My$liwska J, Siebert J, Wieckiewicz J, Hak Ł, Szyndler K, et al. High serum interleukin-18 concentrations in patients with coronary artery disease and type 2 diabetes mellitus. Eur Cytokine Netw. 2005;16(3):177-85.
17. Jin DY, Liu CL, Tang JN, Zhu ZZ, Xuan XX, Zhu XD, et al. Interleukin-18, matrix metalloproteinase-22 and -29 are independent risk factors of human coronary heart disease. 2017;18(8):685-95.
18. Li Q, Kuang Y, Qiu J, Zhang X, Ruan Y, Li Z. The correlation between plasma tissue factor and interleukin 18 and their significance in patients with acute coronary syndrome. Cardiovasc Toxicol. 2015;15(3):276-82.
19. Goetze JP. Markers of activated coagulation in acute coronary syndromes. J Am Coll Cardiol. 2008;51(25):2430-1.
20. Mega JL, Morrow DA, Lemos JA, Mohanavelu S, Cannon CP, Sabatine MS. Thrombus precursor protein and clinical outcomes in patients with acute coronary syndromes. J Am Coll Cardiol. 2008;51(25):2422-9.
21. Laurino JP, Pelletier TE, Eadry R, Kounavis A. Thrombus precursor protein and the measurement of thrombosis in patients with acute chest pain syndrome. Ann Clin Lab Sci. 1997;27(5):338-45.
22. Empana JP, Canoui-Poitrine F, Luc G, Juhan-Vague I, Morange P, Arveiler D, et al. Contribution of novel biomarkers to incident stable angina and acute coronary syndrome: the PRIME Study. Eur Heart J. 2008;29(16):1966-74.
23. Sambola A, Osende J, Hathcock J, Degen M, Nemerson Y, Fuster V, et al. Role of risk factors in the modulation of tissue factor activity and blood thrombogenicity. Circulation. 2003;107(7):973-7.
24. Lee AJ. The role of rheological and haemostatic factors in hypertension. J Hum Hypertens. 1997;11(12):767-76.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Atherosclerosis and Inflammation: Still a Long Way to Go

Ricardo Wang[1,2,3], *Bruno Ramos Nascimento*,[1,3] *Fernando Carvalho Neuenschwander*[2]

Universidade Federal de Minas Gerais, Departamento de Cardiologia Intervencionista,[1] *Belo Horizonte, MG – Brazil*
Hospital Vera Cruz, Departamento de Cardiologia Intervencionista,[2] *Belo Horizonte, MG – Brazil*
Hospital da UNIMEDBH,[3] *Belo Horizonte, MG - Brazil*

Short Editorial related to the article: Role of Interleukin-18 and the Thrombus Precursor Protein in Coronary Artery Disease.

Ever since the initial works by Russell Ross[1] on the importance of inflammation in the development, instability and rupture of the atherosclerotic plaque, which can result in acute coronary syndrome (ACS) or stroke, there has been an increase in publications on the activation pathways, expansion and perpetuation of the inflammatory process, which goes beyond the simple pathophysiological understanding, but mainly in finding specific treatment opportunities, aiming to reduce the so-called "residual risk" (cardiovascular events that occur in patients even when LDL cholesterol levels are within the therapeutic goals).[2] It is estimated that approximately 100,000 new cases of acute myocardial infarction occur each year in Brazil,[3] according to data from DATASUS. If we consider mortality rates of 5-10%, it is expected that approximately 90,000 patients per year will go to secondary prevention. If all patients receive a maximum statin dose, even so, approximately 40%2 will still have a residual risk of events, i.e., 36,000 patients will be at high risk for new cardiovascular events.

This issue brings a study[4] on the role of Interleukin-18 (IL-18) and thrombin precursor protein (TpP) in ACS. TpP is a marker of the coagulation system activation and, in this study, the authors observed an increase in this protein in patients with ACS, a fact that corroborates the importance of the coagulation system in this scenario.[5,6] Anatomopathological studies of plaques have shown that the fibrotic layer rupture is not always accompanied by ACS,[6] as for a "perfect storm" to occur, it is necessary to associate a "vulnerable plaque" with "vulnerable blood" (hypercoagulable state).[5] This study corroborates that TpP can be a useful biomarker for the diagnosis of ACS.

Interleukins are signaling molecules among cells of the inflammatory system, which can induce, proliferate and perpetuate inflammation, but they can also modulate and reduce inflammation. IL-18 is produced by macrophages, in response to the phagocytosis process and it is produced via the caspase system, acts on Th1 cells by stimulating the production of interferon-γ (INF-γ) and Interleukin1β,[7] and its elevation in atherosclerosis is associated with plaque rupture.[8] Plaques considered vulnerable have a necrotic nucleus with a large number of inflammatory cells, mainly macrophages. Inflammation acts by inhibiting smooth muscle cells, which leads to the formation of a thinner fibrous cap, therefore more prone to rupture.

As this is a cross-sectional study, there is a limitation in establishing a causal association; did IL-18 cause ACS or did ACS cause IL-18 elevation? In this context, the elevation of IL-18 may be secondary to myocardial necrosis as suggested by Seta et al.,[9] because during the process of myocardial necrosis and repair, the activation of the inflammatory system occurs, including macrophages. Another limitation of this study is related to the sample, which in addition to being small, was obtained by convenience, which in itself can be a source of bias. The control group can be a problem, as it was selected from patients submitted to coronary angiography, who had no evidence of obstructive angiographic lesion (we recall that, for some reason, they were submitted to an invasive procedure). The coronary angiography has limitations in diagnosing atherosclerosis,[10] because in its initial phase, there is a positive remodeling effect (Glagov effect); plaques with 70% of the total area of the vessel, may present on the angiography as a lesion smaller than 30%.[11] Therefore, the coronary angiography should not be used as the gold standard to rule out atherosclerosis. Moreover, it is known that the plaques that most often result in ACS are mild and inflamed plaques.[5] These limitations could explain the higher levels (although not statistically significant) of IL-18 in the control group, when compared to patients with stable coronary disease in this study (663.25 pg/mL ± 993.93 versus 353.81 pg/mL ± 273.65, respectively, p = NS).

Should IL-18 be blocked for primary prevention? Or should post-infarction ventricular remodeling be improved? Given the complexity of the immune system, and its importance in containing infectious processes and in the cell damage-repair system, its blocking might have consequences. In the case of IL-18, which is part of the caspase system, responsible for fighting intracellular infections, we could observe an increase in infections such as tuberculosis. In the Cantos (Antiinflammatory Therapy with Canakinumab for Atherosclerosis Disease) study, interleukin 1-β blocking was associated with a slight increase in infection rates (not significant), arthritis and fatal cancer (statistically significant).[12] Regarding remodeling, the results are conflicting; interleukin 1β blocking with anakinra was promising,[13] but the blocking of tumor necrosis factor gamma increased mortality. In experimental models, blocking IL-18 has shown to be promising in improving post-infarction remodeling.[14]

Despite the initial enthusiasm for the results of using colchicine and canakinumab, the net benefits are still limited.[12,15] Therefore, it is necessary to investigate other inflammatory pathways. We still have more questions than answers: Which pathway should be blocked? When (primary or secondary prevention)? And at what intensity and for how long?

Keywords

Atherosclerosis/physiopathology; Inflammation; Interleukin-18; Thrombosis; Coronary Artery Disease.

Mailing Address: Ricardo Wang •
Universidade Federal de Minas Gerais, Departamento de Cardiologia Intervencionista – Avenida Alfredo Balena 110, Postal Code 30130-110, Belo Horizonte, MG – Brazil
E-mail: rwang@terra.com.br

DOI: https://doi.org/10.36660/abc.20200219

References

1. Ross R. Atherosclerosis — An inflammatory disease. N Engl J Med. 1999;340(2):115-26.
2. Ridker Paul M. How common is residual inflammatory risk? Circ Res. 2017;120(4):617-9.
3. Wang R, Neuenschwander FC, Lima Filho A, Moreira CM, Santos ES, Reis HJ,et al. Uso de intervenções baseadas em evidências na síndrome coronária aguda. Subanálise do Registro ACCEPT. Arq Bras Cardiol. 2014;102(6):319-26.
4. Interleucina- 18, proteína precursora do trombo DAC. Papel da interleucina 18 e da proteína precursora do trombo na doença arterial coronariana.Arq Bras Cardiol. 2020; 114(4):692-698.
5. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, Rumberger J, et al. From vulnerable plaque to vulnerable patient. Circulation. 2003;108(14):1664-72.
6. Virmani R, Kolodgie Frank D, Burke Allen P, Farb A, Schwartz Stephen M. Lessons From sudden coronary death. Arterioscler Thromb Vasc Biol. 2000;20(5):1262-75.
7. O'Brien LC, Mezzaroma E, Van Tassell BW, Marachetti C, Carbone S, Abbate A, et al.Interleukin-18 as a therapeutic target in acute myocardial infarction and heart failure. Mol Med. 2014 Jun 12;20:221-9.
8. Blankenberg S, Luc G, Ducimetière P, Arveller D, Ferrières J, Amouyel P, et al. Interleukin-18 and the risk of coronary heart disease in european men. Circulation .2003;108(20):2453-9.
9. Seta Y, Kanda T, Tanaka T, Arai M, Sekiguchi K, Yokoyama T, et al. Interleukin 18 in acute myocardial infarction. Heart. 2000;84(6):668.
10. Baim D. Coronary Angiography. In: Baim D, ed. Grossman's Cardiac aatheterization, angiography, and intervention. 7th ed Philadelphia: Lippincott Williams and Wilkins; 2006.p.187-221.
11. Glagov S, Weisenberg E, Zarins CK, Stankunavicius R, Kolettis GJ. Compensatory enlargement of human atherosclerotic coronary arteries. Engl J Med. 1987;316(22):1371-5.
12. Ridker PM, Everett BM, Thuren T, MacFadyen JG, Chang WH, Ballantyne C, et al. Antiinflammatory therapy with Canakinumab for atherosclerotic disease. N Engl J Med. 2017;377(12):1119-31.
13. Frangogiannis NG. Interleukin-1 in cardiac injury, repair, and remodeling: pathophysiologic and translational concepts. Discoveries (Craiova) 2015 Jan-Mar;3(1):e41.
14. Toldo S, Mezzaroma E, Van Tassell BW, Farkas D, Marchetti C, Voelkel NF, et al. Interleukin-1β blockade improves cardiac remodelling after myocardial infarction without interrupting the inflammasome in the mouse. Exp Physiol. 2013;98(3):734-45.
15. Tardif J-C, Kouz S, Waters DD, Bertrand OF, Diaz R, Maggioni AP, et al. Efficacy and safety of low-dmMyocardial infarction. N Engl J Med. 2019; 381(26):2497-505.

Dynamic Balance and Mobility Explain Quality of Life in HFpEF, Outperforming All the Other Physical Fitness Components

Cristine Schmidt,[1,5] Mário Santos,[2,3] Lucimere Bohn,[1] Bruno Miguel Delgado,[4] Daniel Moreira-Gonçalves,[1] Adelino Leite-Moreira,[5] José Oliveira[1]

Faculdade de Desporto da Universidade do Porto (FADEUP), Centro de Investigação em Actividade Física, Saúde e Lazer (CIAFEL),[1] Porto – Portugal
Instituto de Ciências Biomédicas Abel Salazar (ICBAS), Universidade do Porto, Unidade de Pesquisa Multidisciplinar em Biomedicina,[2] Porto – Portugal
Centro Hospitalar do Porto, Departamento de Cardiologia,[3] Porto – Portugal
Centro Hospitalar do Porto,[4] Porto – Portugal
Faculdade de Medicina da Universidade do Porto (FMUP), Unidade de Investigação Cardiovascular (UniC),[5] Porto – Portugal

Abstract

Background: **Physical fitness is an important determinant of quality of life (QoL) in heart failure with preserved ejection fraction (HFpEF) patients. However, how the different physical fitness components correlate with the specific dimensions of QoL in HFpEF patients remains unknown.**

Objective: **To evaluate the association between different physical fitness components and QoL dimensions in HFpEF patients, and, assess which physical fitness components were independently associated to QoL.**

Methods: **Patients with HFpEF were assessed for physical fitness [dynamic balance and mobility (8-foot-up-and go test), upper body strength (handgrip), cardiorespiratory fitness (CRF) (6-minute-walking test) and body composition (body mass index)] and for QoL (Minnesota Living With Heart Failure Questionnaire). Partial correlation was used to verify the association between physical fitness components and QoL dimensions. The determination of independent predictors in QoL dimensions was assessed through stepwise multivariate linear regression analysis. Statistical significance was set at $p<0.05$.**

Results: **Both CRF and dynamic balance and mobility are significantly associated with the total score and physical dimensions of QoL ($p<0.05$), but only dynamic balance and mobility were concomitantly associated with the emotional dimension ($r=0.597$; $p=0.004$). Dynamic balance and mobility were independently associated with total score ($\beta=0.651$; $r^2=0.424$; $p=0.001$), physical ($\beta=0.570$; $r^2=0.324$; $p=0.04$) and emotional ($\beta=0.611$; $r2=0.373$ $p=0.002$) dimensions of QoL.**

Conclusion: **Our data suggests that dynamic balance and mobility better assess QoL than CRF, which is commonly measured in clinical practice. Whether interventions specifically targeting dynamic balance and mobility have different impacts on QoL remains unknown. (Arq Bras Cardiol. 2020; 114(4):701-707)**

Keywords: **Heart Failure/physiopathology; Work-Life Balance/methods; Physical Fitness; Quality of Life; Breathing Exercises; Body Composition.**

Introduction

Heart failure with preserved ejection fraction (HFpEF) accounts for half of all HF cases in the developed world's population.[1] The most common manifestation of the disease is exercise intolerance, which impacts on patients' ability to cope with activities of daily life and reduces their quality of life (QoL).[2] Furthermore, QoL is related with poor outcomes, such as higher frequency of hospital readmission and higher mortality rates.[3] Despite its high prevalence and poor prognosis, HFpEF remains a disease with no approved therapy that improves survival.[4] Therefore, current recommendations for the treatment of these patients highlight the importance to focus on effective therapies capable of alleviating symptoms and meaningfully improve QoL.[5]

Reduced levels of physical fitness are associated with poor QoL in patients with HFpEF.[6,7] Importantly, exercise training has shown to improve physical fitness, together with symptom and QoL improvement.[6,7] Because physical fitness and QoL are mutually related, targeting physical fitness with exercise training programs may be an effective strategy to accomplish the management recommendations of patients with HFpEF.[5] However, physical fitness is a multicomponent (e.g. dynamic

Mailing Address: Cristine Schmidt •
CIAFEL – Faculdade de Desporto da Universidade do Porto. Rua Dr. Plácido da Costa, 91. Postal Code 4200-450, Porto – Portugal
E-mail: schmidtcristine@gmail.com
Manuscript received February 06, 2019, revised manuscript June 10, 2019, accepted June 23, 2019

DOI: https://doi.org/10.36660/abc.20190080

balance and mobility, muscular fitness, cardiorespiratory fitness (CRF) and body composition)[8] and, in parallel, QoL is a multidimensional construct (e.g. general, emotional and physical).[9] Until now, it remains unknown how the different components of physical fitness correlate with the specific dimensions of QoL in HFpEF patients. To date, it has only been demonstrated that a higher CRF is associated with a better QoL, mainly regarding the physical dimension.[7,10] However, the influence of other physical fitness components on QoL dimensions is relatively unknown. Therefore, the clarification of this issue might have important clinical implications in the design of specific interventional programs for HFpEF patients targeting the physical fitness component, which most impacts on QoL, whether overall or one of its depressed dimensions.

Therefore, the aims of the present study are twofold: i) to evaluate the association between different physical fitness components (CRP, upper body strength, dynamic balance and mobility, and body composition) and the QoL dimensions (total, physical and emotional) in HFpEF patients, and ii) to assess which of the physical fitness components are independently associated to different dimensions of QoL in this specific population.

Methods

Study design

This is a cross-sectional study conducted in a Portuguese public hospital (*Centro Hospitalar do Porto - Hospital de Santo Antonio*, Porto) with a convenience sample of HFpEF. Inclusion criteria was diagnosis of HFpEF according to the European Society of Cardiology guidelines.[11] Patients were excluded if they presented with unstable angina, acute coronary syndrome as primary diagnosis, symptomatic severe aortic stenosis, acute pulmonary embolism, acute myocarditis, decompensated heart failure, uncontrolled hypertension, complex ventricular arrhythmias, severe renal dysfunction, severe chronic obstructive pulmonary disease, medical or orthopedic conditions that precluded independent ambulation and exercise testing.

Patients who were potentially eligible to participate in the study were identified from the clinical files of the hospital cardiology department. A total of 30 patients were invited through phone calls by a cardiologist. Of those, 24 patients (17 women and 7 men) accepted to take part in the study. The study was approved by the Ethics Committee of *Centro Hospitalar do Porto - Hospital de Santo Antonio* (*N/S:* 2015.125) and met the ethical standards of the Declaration of Helsinki.

Data were collected from November 2016 to September 2017 during a single day in the hospital.

Data collection

Blood pressure

A trained researcher performed blood pressure measurements after a 10 minute-rest in the sitting position. Blood pressure was assessed (Colin, BP 8800; Critikron, Inc., USA) in both arms, and the arm showing the highest BP was used. SBP and DBP were computed as the average of 3 readings, with a 2-minute interval between them. Additional readings were performed when differences between readings exceeded 5 mmHg.[12]

Blood collection and biochemical determinations

Peripheral venous blood (15 mL) was collected into an EDTA tube. The EDTA tubes were immediately placed on ice and allowed to clot for 30 minutes before centrifugation for 15 minutes at 1000xg. The plasma was aliquoted and stored at -80ºC for biochemical analysis. Brain Natriuretic Peptide (BNP) was quantified in a certified laboratory using chemiluminescent microparticle immunoassay (ARCHITECT BNP).

Anthropometric and body composition measures

Body height (cm) was measured in the upright position using a stadiometer (Holtain Ltd., Crymmych, UK).[13] Weight (kg), body mass index (BMI; kg·m^2), fat mass (%) and free fat mass (kg) were measured with patients wearing light clothes, using an electronic segmental body composition analyzer (Tanita, BC-418, Tokyo, Japan). Fat mass and free fat mass were measured using bioelectrical impedance. Patients were asked to fast for 10-12 hours, avoid vigorous physical exercise and alcohol intake before being measured. Waist circumference (cm) was measured at the midpoint between the lowest rib and the iliac crest at the end of normal expiration.[14] Obesity was determined as BMI equal or higher than 30 kg/m^2.[15]

Functional classification

Patients were classified by the physician into subgroups based on their symptoms using the New York Heart Association (NYHA) functional class. Patients' symptoms are based on how much they were limited during physical activity (class I to IV).[16]

Echocardiography Evaluation

Supine transthoracic echocardiography was performed using a cardiovascular ultrasound model Vivid E95® (GE Healthcare). All quantitative echocardiographic measurements were performed by a single reader blinded to the results of the other evaluations, using a computerized off-line analysis station. Peak early diastolic tissue velocity was measured at the septal and lateral mitral annulus. Mitral inflow velocity was assessed by pulsed wave Doppler at the apical 4-chamber view, positioning the sample volume at the tip of the mitral leaflets. E/e' ratio was calculated as E wave divided by e' velocities. LV mass was estimated based on LV linear dimensions and indexed to body surface area, as recommended by ESC guidelines.17 LV hypertrophy was defined as LV mass indexed to body surface area (LV mass index) >115 g·m^2 in men or >95 g·m^2 in women. LV volumes were estimated by the modified Simpson method using the apical 4- and 2-chamber views, and LVEF was derived from volumes in the standard manner. LA volume was estimated by the method of disks using apical 4- and 2-chamber views at an end-systolic frame preceding mitral valve opening and was indexed to body surface area to derive LA volume index.

Physical Fitness

Dynamic balance and mobility. It was assessed with the 8-foot up and go (8FUG) test.[18] The patient starts the evaluation in the sitting position. After a signal, the patient must stand up, walk 8 feet (2.44m), make a turn around a cone, and return back to the initial position as fast as possible.[18] The patients tried to perform the test twice. Time (in seconds) to complete each trial was measured with a stopwatch and the result considered was the shorter time.[19]

Upper body strength. Grip strength (kg) was isometrically measured using a Lafayette Instrument Hand dynamometer (*Model 78010, 78011, Indiana, USA*). Both arms were measured 3 times while patients were seated, with shoulder adducted and neutrally rotated, the elbow flexed at 90°, and the forearm and wrist in a neutral position. The average between attempts was used as final score for each arm.[19]

Cardiorespiratory fitness with pulmonary gas exchange assessment. It was assessed by the 6-minute walk test (6MWT) in a 25-m-long unobstructed corridor. Participants were instructed to walk the maximal distance in 6 minutes time. Resting stops were allowed when patients felt it to be necessary. The 6MWT was performed wearing a portable gas analyzer (K4b2, Cosmed, Rome, Italy) and a heart rate monitor (Polar Electro Oy, Kempele, Finland). Oxygen uptake (VO2; mL·min-1·kg-1) and heart rate (HR; bpm) were measured directly and continuously. Respiratory and HR measurements were collected in a breath-by-breath and beat-to-beat basis, respectively, and then, data were averaged over 5-s intervals. Data was calculated as the average of measures taken during the test total duration (6 minutes).

Health-related quality of life

Health-related QoL was measured through an interview using the Minnesota Living With Heart Failure Questionnaire (MLWHFQ). The MLHFQ encompasses 21 questions, whose purpose is to determine how disease affects the physical, psychological and socioeconomic conditions of the patients during the previous month.[20] The questions include symptoms and signs relevant to disease, levels of physical activity, work, social interaction, sexual activity, and emotions. The MLHFQ total score range from 0 to 105 (no impairment to maximum impairment). Two other scores can be determined: the physical dimension (8 items, 0–40), and the emotional dimension (5 items, 0–25). A higher MLHFQ score means a worse QoL. Answers options ranges from 0 (none) to 5 (very much), where 0 represents no limitation and 105 represents maximal limitation.

Statistical analyses

Data normality was verified by Shapiro-Wilk test. Non-normally distributed variables were transformed into a natural logarithm (weight, fat mass, free fat mass, 8FUG, MLHFQ total score, MLHFQ physical and MLHFQ emotional) for subsequent analysis and then transformed back to the original scale for the purpose of clarity. Data are expressed as mean ± standard deviation. Categorical data are reported as absolute values and percentages. Pearson's correlation was used to analyze the association between physical fitness components (dynamic balance and mobility, upper body strength, CRF and BMI) aiming to verify collinearity between variables ($r>0.75$). Partial correlation (adjusted for age, gender and NYHA class) was used to assess the association between physical fitness components and QoL dimensions. A multivariate linear regression analysis, with stepwise selection of variables, was performed to determine the association between QoL dimensions and age, gender, NYHA functional class and physical fitness components, which were identified as potential independent predictors of QoL. The statistical analysis was performed using the IBM SPSS 24 software (SPSS, USA), and the statistical significance was set at $p<0.05$.

Results

Patients' characteristics

The demographic and clinical characteristics of patients are shown in Table 1. The patients' mean age was 76±6 years old, ranging from 59 to 85 years, and 71% (n=17) were females. Hypertension was the most prevalent comorbidity (n=22, 92%), followed by dyslipidemia (n=17, 71%) and obesity (n=14, 58%). Regarding the NYHA functional class, 79% (n=19) of all patients were classified as class II. The average BNP level was 288.9±191.5 pg·mL-1. Regarding cardiac function, the mean ejection fraction was 60±6%, 23% (n=6) of patients had E/e` >15, while 90% (n=22) had LAVI >34 mL·m^2. All patients had left ventricular hypertrophy.

Quality of life

The score of total MLHFQ scale was 26±24, whereas the physical and emotional MLHFQ subscales' scores were 12±13, and 5±7, respectively.

Physical fitness

Overall, the 6MWT distance, 8FUG and handgrip results were 312±90 meters, 10.9±3.6 seconds, and 18.6±7.1kg, respectively. The mean VO_2 during the test was 11.2± 2.3 mL·min-1·kg-1. A bivariate correlation between physical fitness components showed that the 8FUG test was inversely correlated with handgrip ($r=-0.47$; $p=0.01$) and 6MWT distance ($r=-0.81$; $p>0.001$) (Table 2).

Association between physical fitness and quality of life

A partial correlation between QoL dimensions and physical fitness components are shown in Table 3. A better MLHFQ total score was directly correlated with 8FUG ($r=0.563$; $p=0.008$) and inversely correlated with 6MWT ($r=-0.539$; $p=0.012$) test results. Regarding MLHFQ physical, it was directly correlated with 8FUG ($r=0.529$; $p=0.014$) and inversely correlated with 6MWT ($r=-0.478$ $p=0.028$). Finally, MLHFQ emotional was directly correlated with 8FUG ($r=0.597$; $p=0.004$).

Table 4 shows the multivariate regression analysis for QoL dimensions. All models were adjusted for age, gender and NHYA functional class as potential confounders. For MLHFQ total score, the 8FUG was the only physical fitness parameter that remained an independent predictor ($\beta=0.651$; $p=0.001$). Similarly, for MLHFQ physical dimension, the

Table 1 – General patients' characteristics

	All (n=24)
Sociodemographic characteristics	
Age (years)	76 ± 6.1
Female (n) (%)	17 (71%)
Anthropometrics	
Weight (Kg)	71.8 ± 15.9
Waist circumference (cm)	100.9 ± 12.6
Body fat (%)	36.1±6.5
Free fat mass (kg)	45.4±9.7
Risk factors, n (%)	
Obesity (BMI ≥ 30 kg/m2)	14 (58%)
Ex-smoker	4 (17%)
Hypertension	22 (92%)
Dyslipidemia	17 (71%)
Type 2 diabetes	2 (8%)
Pre-diabetic	9 (38%)
Atrial fibrillation	12 (50%)
Atrial fibrillation (paroxysmal)	4 (17%)
COPD	2 (8%)
Obstructive sleep apnea	6 (25%)
Clinical signs	
Resting HR (bpm)	72 ± 16
SBP (mmHg)	136 ± 19
DBP (mmHg)	70 ± 14
BNP (pg/mL)	289 ± 192
NYHA class II	19 (79%)
NYHA class III	4 (17%)
Medication (%)	
ACE-i/ARB	17 (71%)
ß-Blocker	20 (83%)
Loop diuretics	18 (75%)
Statin	16 (67%)
Digoxin	4 (17%)
MRAs	2 (8%)
Cardiac Function	
LVEF (%)	60 ± 6.3
E/e´	12.2 ± 3.1
E/A	1.0 ± 0.5
LVMI (gm/m^2)	231.3 ± 94.5
LAVI (mL/m^2)	44.2 ± 11.7

COPD: chronic obstructive pulmonary disease; HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; BNP: brain natriuretic peptide; NYHA: New York Heart Association; ACEi/ARB: angiotensin-converting enzyme inhibitor and angiotensin receptor blocker; MRAs: mineralocorticoid receptor antagonists; LVEF: left ventricle ejection fraction; E/e´: ratio of early mitral inflow velocity and mitral annular early diastolic velocity; E/A: mitral ratio of peak early to late diastolic filing velocity; LVMI: left ventricle mass index; LAVI: left atrium volume index.

8FUG was the single physical fitness component that remained an independent predictor (β=0.570; p=0.04). Finally, for MLHFQ emotional, the 8FUG was the single physical fitness component that remained an independent predictor (β=0.611; p=0.002).

Discussion

The data provided by our study indicates that physical fitness is positively correlated with QoL in HFpEF patients. In addition, dynamic balance and mobility was the only physical fitness component that was independently associated with QoL total score, and physical and emotional dimensions. These findings suggest that this specific component of physical fitness outperforms CRF in assessing HFpEF patients' QoL. In addition, it highlights the need to study interventions specifically targeting these fitness components to enhance QoL gains.

Despite the high prevalence and poor prognosis of HFpEF, evidence-based therapies aimed at effectively reducing morbidity or mortality remains to be developed.[4] These patients are often characterized by poor QoL[21] and current treatment guidelines highlight the importance of aiming to improve patients' well-being.[5] Physical fitness is a multicomponent construct[8] and several studies show it is a major determinant of QoL in HFpEF.[6,7] Our results corroborate this finding, as we observed that QoL total score strongly correlated with physical fitness (e.g. dynamic balance and mobility, and CRF) in HFpEF patients.

Because physical fitness might influence QoL, strategies targeting physical fitness might potentially improve QoL, independent of further health benefits.[22] A recent meta-analysis showed that the combination of endurance exercise training together with cardiovascular drugs provide a clinically relevant improvement in both exercise capacity and QoL in HFpEF patients.[23] However, physical fitness and QoL are multicomponent and multidimensional constructs, respectively, and it is crucial to ascertain which dimension/component is better related to each other to maximize possible QoL improvements.

Previous studies have shown that CRF is mainly associated with the physical dimension, but not necessarily with the total score or emotional dimension of QoL.[7,10] We observed that CRF (assessed by the 6MWT) and dynamic balance and mobility (assessed by 8FUG) were both associated with the physical dimensions of QoL. Moreover, dynamic balance and mobility were the only physical fitness components associated with the QoL emotional dimension, while upper body strength (assessed by handgrip) and body composition were not associated with any dimension. In addition, multivariate analysis revealed that the dynamic balance and mobility was the only physical fitness component independently associated with all QoL dimensions, explaining 42% of variance in the total score QoL, 32% of the physical dimension and 37% of the emotional dimension of QoL. Thus, of all physical fitness components, dynamic balance and mobility seems to be the one that better assess QoL in HFpEF patients.

Collectively, our data suggest that improving the specific physical fitness component of dynamic balance and mobility

Table 2 – Bivariate correlation between physical fitness parameters

	Dynamic balance and mobility	Upper body strength	Cardiorespiratory fitness	Body composition		
	8FUG	Handgrip	6MWT	BMI	% FM	FFM
8FUG		-0.478 (0.018)	-0.816 (<0.00)	-0.030 (0.888)	0.184 (0.389)	-0.221 (0.299)
Handgrip	-0.478 (0.018)		0.390 (0.060)	0.017 (0.939)	-0.362 (0.082)	0.284 (0.179)
6MWT	-0.816 (<0.00)	0.390 (0.060)		-0.074 (0.733)	-0.161 (0.453)	0.010 (0.964)
BMI	-0.030 (0.888)	0.017 (0.939)	-0.074 (0.733)		0.566 (0.004)	0.533 (0.007)
Fat Mass	0.184 (0.389)	-0.362 (0.082)	-0.161 (0.453)	0.566 (0.004)		-0.258 (0.224)
FFM	-0.221 (0.299)	0.284 (0.179)	0.010 (0.964)	0.533 (0.007)	-0.258 (0.224)	

8FUG: 8-foot up and go test; 6MWT: six-minute walk test; BMI: body mass index; FM: fat mass; FFM: free fat mass. Data are r (p).

will eventually result in the greatest QoL improvement. The 8FUG reflects the specific demands of activities, such as standing up from a sitting position, walking short distances, turning, stopping and sitting down.[24] This might be explained by the wide range of physical abilities, including lower body strength, dynamic balance, walking ability, agility and gait speed[8] involved in the 8FUG. These abilities are also required during the normal daily tasks of an independent and autonomous life, especially among the elderly.[25] Future studies (e.g. longitudinal training programs) should assess if an exercise training program focused on enhancing motor abilities (e.g. dynamic balance and mobility) can improve the physical and emotional components of QoL in HFpEF in comparison to current standard ones.

Study limitations

The small sample size, cross-sectional and convenience sampling design of our study limits the generalization of our results. Despite that, our sample assembles the usual clinical features of HFpEF population reported in large studies[5] with a higher prevalence of elderly women and a higher prevalence of comorbidities. Further prospective cohort studies with a larger sample size are needed to strengthen or refute our conclusions that dynamic balance and mobility are more efficient in assessing HFpEF patients' QoL.

Conclusion

Overall, our findings indicate that both CRF and dynamic balance and mobility are directly associated with the QoL total score and physical dimensions in patients with HFpEF, but only dynamic balance and mobility were concomitantly associated with the emotional dimension. Multivariate analyses revealed that dynamic balance and mobility outperforms CRF in assessing HFpEF patients' QoL. In addition, our data suggests that specifically targeting motor agility and balance may be an important strategy to enhance QoL gains in all dimensions.

Author contributions

Conception and design of the research and obtaining financing: Schmidt C, Santos M, Moreira-Gonçalves D, Leite-Moreira A, Oliveira J; Acquisition of data: Schmidt C, Santos M, Bohn L, Delgado BM, Moreira-Gonçalves D; Analysis and interpretation of the data, writing of the manuscript and critical revision of the manuscript for intellectual content: Schmidt C, Santos M, Bohn L, Delgado BM, Moreira-Gonçalves D, Leite-Moreira A, Oliveira J; Statistical analysis: Schmidt C, Santos M, Bohn L, Delgado BM, Moreira-Gonçalves D, Oliveira J.

Potential Conflict of Interest

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

Sources of Funding

CIAFEL is supported by FCT under Grant [UID/DTP/00617/2019]. UnIC is supported by FCT under Grant [UID/IC/00051/2019] and [UID/DTP/00617/2019]. This work was supported by the project [PTDC/MEC-CAR/30011/2017] [POCI-01-0145-FEDER-030011]. Cristine Schmidt was supported by individual grant from CAPES [BEX 0554/14-6].

Study Association

This article is part of the thesis of Doctoral submitted by Cristine Schmidt, from Faculdade de Desporto da Universidade do Porto.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Centro Hospitalar do Porto/HSA under the protocol number 2015-125. 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.

Table 3 – Partial correlation between quality of life dimensions and physical fitness components

	Dynamic balance and mobility	Upper body strength	Cardiorespiratory fitness	Body composition		
	8FUG	Handgrip	6MWT	BMI	% FM	FFM
MLHFQ total	0.563 (0.008)	-0.118 (0.611)	-0.539 (0.012)	0.208 (0.366)	-0.012 (0.957)	0.372 (0.097)
MLHFQ physical	0.529 (0.014)	-0.261 (0.254)	-0.478 (0.028)	0.260 (0.255)	-0.027 (0.909)	0.353 (0.116)
MLHFQ emotional	0.597 (0.004)	-0.023 (0.919)	-0.394 (0.077)	0.199 (0.388)	0.002 (0.993)	0.297 (0.191)

Adjusted for age, gender and NYHA functional class. 8FUG, 8-foot up and go test. 6MWT, six-minute walk test. BMI, body mass index. FM, fat mass. FFM, free fat mass. MLHFQ, Minnesota Living with Heart Failure Questionnaire. Data are r (p).

Table 4 – Stepwise regression analysis assessing which physical fitness components were independently associated with specific quality of life dimensions

	β	B	R2	p
MLHFQ total				
Ln 8FUG	0.651	5.015	0.424	0.001
MLHFQ physical				
Ln 8FUG	0.570	3.788	0.324	0.040
MLHFQ emotional				
Ln 8FUG	0.611	3.003	0.373	0.002

Ln 8FUG: natural logarithm of 8-foot up and go test; MLHFQ: Minnesota Living with Heart Failure Questionnaire; β: standardized regression coefficient; B: non-standardized regression coefficient; R^2: adjusted coefficient of determination.

References

1. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017;14(10):591-602.
2. Edelmann F, Stahrenberg R, Polzin F, Kockskamper A, Dungen HD, Duvinage A, et al. Impaired physical quality of life in patients with diastolic dysfunction associates more strongly with neurohumoral activation than with echocardiographic parameters: quality of life in diastolic dysfunction. Am Heart J. 2011;161(4):797-804.
3. Rodriguez-Artalejo F, Guallar-Castillon P, Pascual CR, Otero CM, Montes AO, Garcia AN, et al. Health-related quality of life as a predictor of hospital readmission and death among patients with heart failure. Arch Intern Med. 2005;165(11):1274-9.
4. Holland DJ, Kumbhani DJ, Ahmed SH, Marwick TH. Effects of treatment on exercise tolerance, cardiac function, and mortality in heart failure with preserved ejection fraction. A meta-analysis. J Am Coll Cardiol. 2011;57(16):1676-86.
5. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200.
6. Nolte K, Herrmann-Lingen C, Wachter R, Gelbrich G, Dungen HD, Duvinage A, et al. Effects of exercise training on different quality of life dimensions in heart failure with preserved ejection fraction: the Ex-DHF-P trial. Eur J Prev Cardiol. 2015;22(5):582-93.
7. Kitzman DW, Brubaker PH, Morgan TM, Stewart KP, Little WC. Exercise training in older patients with heart failure and preserved ejection fraction: a randomized, controlled, single-blind trial. Circ Heart Fail. 2010;3(6):659-67.
8. Rikli RE, Jones CJ. Development and validation of criterion-referenced clinically relevant fitness standards for maintaining physical independence in later years. Gerontologist. 2013;53(2):255-67.
9. The World Health Organization Quality of Life Assessment Group. The World Health Organization Quality of Life Assessment (WHOQOL): development and general psychometric properties. Soc Sci Med. 1998;46(12):1569-85.
10. Edelmann F, Gelbrich G, Dungen HD, Frohling S, Wachter R, Stahrenberg R, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. J Am Coll Cardiol. 2011;58(17):1780-91.
11. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, et al. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012. European journal of heart failure. 2012;14(8):803-69.
12. Mancia G, Grassi G, Redon J. Manual of Hypertension of the European Society of Hypertension. 2nd ed. Boca Raton:CRC Press; 2014.
13. Lohman TG, A.F. Roche, and R. Martorell. Anthropometric Standardization Reference Manual. Champaign, IL: Human Kinetics Books; 1988.
14. Riley L, Guthold R, Cowan M, Savin S, Bhatti L, Armstrong T, et al. The World Health Organization STEPwise Approach to Noncommunicable Disease Risk-Factor Surveillance: Methods, Challenges, and Opportunities. Am J Public Health. 2016;106(1):74-8.
15. WHO. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. World Health Organ Tech Rep Ser. 2000;894:1-253.
16. Dolgin M. Nomenclature and criteria for diagnosis of diseases of the heart and great vessels. The Criteria Committee of the New York Heart Association. 9 ed. Boston: Little, Brown & Co; 1994. 253-6 p.

17. Lang RM, Badano LP, Mor-Avi V, Afilalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2015;16(3):233-70.

18. Jones CJ, & Rikli, R. E. Measuring functional. The Journal on active aging. 2002;1:24-30.

19. MacDermid J, Solomon G, Valdes KU. Clinical Assessment Recommendations: American Society of Hand Therapists; 2015.

20. Rector TS, Cohn JN. Assessment of patient outcome with the Minnesota Living with Heart Failure questionnaire: reliability and validity during a randomized, double-blind, placebo-controlled trial of pimobendan. Pimobendan Multicenter Research Group. Am Heart J. 1992;124(4):1017-25.

21. Hoekstra T, Lesman-Leegte I, van Veldhuisen DJ, Sanderman R, Jaarsma T. Quality of life is impaired similarly in heart failure patients with preserved and reduced ejection fraction. Eur J Heart Fail. 2011;13(9):1013-8.

22. Pandey A, Parashar A, Kumbhani D, Agarwal S, Garg J, Kitzman D, et al. Exercise training in patients with heart failure and preserved ejection fraction: meta-analysis of randomized control trials. Circ Heart Fail. 2015;8(1):33-40.

23. Fukuta H, Goto T, Wakami K, Ohte N. Effects of drug and exercise intervention on functional capacity and quality of life in heart failure with preserved ejection fraction: A meta-analysis of randomized controlled trials. Eur J Prev Cardiol. 2016;23(1):78-85.

24. Wall JC, Bell C, Campbell S, Davis J. The Timed Get-up-and-Go test revisited: measurement of the component tasks. J Rehabil Res Dev. 2000;37(1):109-13.

25. Mlinac ME, Feng MC. Assessment of Activities of Daily Living, Self-Care, and Independence. Arch Clin Neuropsychol. 2016;31(6):506-16.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Time to Include Balance Training in the Cardiac Rehabilitation Programs of Patients with Heart Failure with Preserved Ejection Fraction

Fernando Ribeiro[1]

Instituto de Biomedicina (iBiMED) - Escola Superior de Saúde - Universidade de Aveiro,[1] *Aveiro – Portugal*

Short editorial related to the article: Dynamic Balance and Mobility Explain Quality of Life in HFpEF, Outperforming All the Other Physical Fitness Components

The burden of heart failure exerts a significant personal, social and economic impact not only on patients and their families but also on society (including health care systems). Heart failure is a chronic, progressive condition affecting a huge amount of individuals worldwide (>37.7 million cases estimated in 2010).[1] It is characterized by typical symptoms (e.g. breathlessness and fatigue) that may be accompanied by signs (e.g. peripheral edema) caused by cardiac abnormalities – structural and/or functional –, resulting in reduced cardiac output and/or elevated intracardiac pressures at rest or during stress.[2] Heart failure has been categorized in heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF) according to the left ventricular ejection fraction.[2]

Heart failure with preserved ejection fraction has become an increasingly recognized phenotype; despite being primarily considered a condition that affects old-age individuals, it represents approximately half of all cases of heart failure.[3,4] Despite the available pharmacological and device therapies, heart failure patients' prognosis, quality of life, and 5-year survival remain poor[5] and similar across all heart failure categories.[4-6]

Heart failure is a frequent cause of hospitalization, especially in older adults.[7] Older adults with heart failure hospitalized for cardiovascular causes, namely acute decompensated heart failure, are usually frail and have a poor quality of life and severe impairments in several components of physical fitness including exercise capacity, muscle strength, balance and mobility.[8] These impairments may help explain why the hospitalizations of patients with HFpEF are often related to non-cardiovascular causes.[9] Lower physical fitness, namely balance and functional mobility impairments, and the use of some medications (e.g. digoxin) increases the risk of falling in old age patients with heart failure. It was reported not only an association between heart failure and increased fall risk but also a much higher fall rate (43%) in heart failure patients compared to patients with coronary artery disease (34%) or diabetes mellitus (28%).[10,11]

Keywords

Heart Failure/physiopathology; Cardiac Rehabilitation; Stroke Volume; Cardiac Output; Hospitalization

Mailing Address: Fernando Ribeiro •
Universidade de Aveiro - Edifício 30 Agras do Crasto - Campus Universitário de Santiago. 3810-193, Aveiro – Portugal
E-mail: fernando.ribeiro@ua.pt

DOI: https://doi.org/10.36660/abc.20200157

Physical fitness is a construct of health-related (body composition, cardiorespiratory endurance, flexibility, muscular endurance, power) and skill-related attributes (balance, agility, coordination, speed, reaction time) that refers to the ability of our body systems to work together efficiently. In this issue of the journal, Schmidt et al.[12] explores this issue in an elderly (mean age 76 ± 6 years old) cohort of patients with HFpEF. The authors assessed the association between different components of physical fitness – exercise capacity, handgrip strength, dynamic balance and mobility, and body composition – and dimensions of quality of life of HFpEF patients. They also examined which physical fitness components were independently related to health-related quality of life. The authors carried out a cross-sectional study with a convenience sample of 24 patients (17 women and 7 men), 79% of them with a New York Heart Association (NYHA) functional class II (n=19) and only four patients (21%) with functional class III. They found a significant association between the 6-minute walk test (6MWT) distance (exercise capacity) and the score in the 8-foot up and go test (dynamic balance and mobility) with the total score and physical dimension score of the Minnesota Living With Heart Failure Questionnaire (health-related quality of life), but only dynamic balance and mobility was concomitantly associated with the emotional dimension. Interestingly, only the performance in the 8-foot up and go test (dynamic balance and mobility) was associated with quality of life – total score, physical and emotional dimensions – after adjusting for age, gender and NYHA functional class. Those patients with better balance also reported enhanced quality of life. In this study, peak oxygen consumption during cardiopulmonary exercise test was not assessed, and it is therefore not possible to determine whether there is an association between a maximal or symptom-limited measure of exercise capacity and quality of life, as well as whether balance is still associated with quality of life when also controlling for peak oxygen consumption. Despite the small sample size predominantly composed by women (71%) with mild functional impairment and the convenience sampling, this study generated interesting data that can be used to inform future and larger studies in this area. A secondary analysis of the RELAX and NEAT-HFpEF Trials recently published,[13] assessed sex differences in exercise capacity (6MWT) and quality of life (Minnesota Living with Heart Failure Questionnaire) in 323 patients with HFpEF (158 men and 165 women) and found different determinants of quality of life between women and men. Interestingly, quality of life was associated with diastolic dysfunction, ischemic heart disease, and exercise capacity in men, while in women-only body mass index and age predicted quality of life. Could dynamic balance and mobility be one of the determinants of quality of life in women with HFpEF?

Short Editorial

The study of Schmidt et al.[12] shed some light on this issue, as they recruited a sample composed predominantly by women (71%), used the same tools to assess the quality of life and exercise capacity, and concluded that dynamic balance and mobility outperforms exercise capacity in capturing HFpEF patients' quality of life. Collectively, these findings reinforce the importance of carrying out studies in women with HFpEF to identify determinants of their quality of life.

The high mortality, morbidity, cardiovascular and heart failure readmission rates, and health care use and costs associated with the increase in heart failure prevalence clearly signal the need to improve treatment strategies. The study of Schmidt et al[12] certainly leaves the reader with the feeling that there is an important aspect of HFpEF care that could be missing in old age patients. As an independent predictor of quality of life, should all old age patients be tested for dynamic balance and mobility? Balance deficits are potentially treatable, and identifying and treating such deficits may improve patients' quality of life. Further investigation with larger sample size is needed to strengthen or refute Schmidt et al.[12] conclusions and help clinicians decide whether to test or not balance daily.

The study of Schmidt et al.[12] by suggesting dynamic balance and mobility as the most important determinant of quality of life (both physical and emotional dimensions), raises also another pertinent question: is it time to include balance training in the cardiac rehabilitation programs of patients with HFpEF? Exercise-based cardiac rehabilitation is a class 1A recommendation for heart failure patients;[2] in patients with HFpEF the benefits are multi-dimensional, for instance, an exercise-based cardiac rehabilitation program improves exercise capacity, diastolic function, and quality of life.[14-16] Nonetheless, traditional cardiac rehabilitation programs do not fully address the multi-domain functional impairments common in older patients with HFpEF, particularly balance and functional mobility impairments. The response to the above-mentioned question could be given in studies assessing the impact of multi-domain cardiac rehabilitation programs designed to also improve balance and functional mobility (in addition to other goals such as improve exercise capacity) administered by a multi-disciplinary team; and, assessing whether a program encompassing specific balance and functional mobility exercises in addition to aerobic and resistance exercise is more effective to improve balance and quality of life, decrease the risk and rate of fall, and to reduce cardiovascular and non-cardiovascular hospitalizations.

In summary, the current contribution by Schmidt et al.[12] in this issue of ABC raises awareness and provides evidence to advocate assessing dynamic balance and mobility in old age patients with HFpEF. However, before this is implemented in clinical routine, their findings need to be strengthened in future studies.

Acknowledgments

iBiMED is a research unit supported by the Portuguese Foundation for Science and Technology (REF: UID/BIM/04501/2020) and FEDER/ Compete2020 funds.

References

1. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* .2012; 380(9859): 2163-96.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2016; 18(8): 891-975.
3. Owan TE , Redfield MM. Epidemiology of diastolic heart failure. *Prog Cardiovasc Dis*. 2005; 47(5): 320-32.
4. Shah KS, Xu H, Matsouaka RA, Bhatt DL, Heidenreich PA, Hernandez AF, et al. Heart Failure With Preserved, Borderline, and Reduced Ejection Fraction: 5-Year Outcomes. *J Am Coll Cardiol*. 2017;70(20):2476-86.
5. Go AS, Mozaffarian D, Roger VL, Berry JD, Blaha MJ, Benjamin EJ, et al. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. *Circulation*. 2014; 129(3): e28-e292.
6. Cheng RK, Cox M, Neely ML,Heidenreich PA, Bhatt DL, Eapen Z, et al. Outcomes in patients with heart failure with preserved, borderline, and reduced ejection fraction in the Medicare population. *Am Heart J*. 2014; 168(5):721-30.
7. Chen J, Dharmarajan K, Wang Y,Krumholtz HM. National trends in heart failure hospital stay rates, 2001 to 2009. *J Am Coll Cardiol*. 2013; 61(10):1078-88.
8. Reeves GR, Whellan DJ, Patel MJ,O'Connor CM, Duncan P, Eggebeen JD, et al. Comparison of Frequency of Frailty and Severely Impaired Physical Function in Patients >/=60 Years Hospitalized With Acute Decompensated Heart Failure Versus Chronic Stable Heart Failure With Reduced and Preserved Left Ventricular Ejection Fraction. *Am J Cardiol*.2016;117(12):1953-8.
9- Gerber Y, Weston SA, Redfield MM, Chamberlain Am, Manemann SM,Jiang R, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. *JAMA Intern Med* .2015; 175(6): 996-1004.
10. Lee PG, Cigolle C, Blaum C. The co-occurrence of chronic diseases and geriatric syndromes: the health and retirement study. *J Am Geriatr Soc*. 2009;57(3) 57: 511-6.
11. Lee K, Pressler SJ , Titler M. Falls in Patients With Heart Failure: A Systematic Review. *J Cardiovasc Nurs*. 2016; 31(6): 555-61.
12. Schmidt C, Santos M, Bohn L, Delgado BM, Moreira-Gonçalves D, Leite-Moreira A, Oliveira J. Equilíbrio Dinâmico e Mobilidade Explicam a Qualidade de Vida na ICFEP, Superando Todos os Outros Componentes da Aptidão Física. Arq Bras Cardiol. 2020; 114(4):701-707.
13. Honigberg MC, Lau ES, Jones AD,Coles A,Redfield MM, Lewis GD, et al. Sex Differences in Exercise Capacity and Quality of Life in Heart Failure with Preserved Ejection Fraction: a Secondary Analysis of the RELAX and NEAT-HFpEF Trials. *J Card Fail* .2020 ;28(3):276-80.
14. Alves AJ, Ribeiro F, Goldhammer E, Rivlin Y, Rosenschein U, Viana JL, et al. Exercise Training Improves Diastolic Function in Heart Failure Patients. *Med Sci Sports Exerc*. 2012; 44(5):776-85.

15. Edelmann F, Gelbrich G, Dungen HD, Frohling S, Wachter R, Stahrenberg R, et al. Exercise training improves exercise capacity and diastolic function in patients with heart failure with preserved ejection fraction: results of the Ex-DHF (Exercise training in Diastolic Heart Failure) pilot study. *J Am Coll Cardiol*.2011;58(17):1780-91.

16. Nolte K, Herrmann-Lingen C, Wachter R, Gelbrich G, Dungen HD, Duvinage A, et al. Effects of exercise training on different quality of life dimensions in heart failure with preserved ejection fraction: the Ex-DHF-P trial. *Eur J Prev Cardiol* . 2015; 22(5): 582-93.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Original Article

Absence of Nocturnal Fall in Blood Pressure Detected by Ambulatory Blood Pressure Monitoring in Acute Chagas Disease Patients with Oral Infection

Dilma do S. M. de Souza,[1] Céres Larissa Barbosa de Oliveira,[1] Brenda Gonçalves Maciel,[1] Maria Tereza Figueiredo,[1] Henrique Tria Bianco,[2] Francisco A. H. Fonseca,[2] Maria Cristina Izar,[2] Rui M. S. Póvoa[2]

Universidade Federal do Pará,[1] Belém, PA - Brazil

Universidade Federal de São Paulo – Escola Paulista de Medicina,[2] São Paulo, SP - Brazil

Abstract

Background: The involvement of the autonomic nervous system is one of the mechanisms proposed to explain the progression of myocardial lesion in Chagas disease. Evidences have shown changes in sympathetic and parasympathetic nervous system since the acute phase of the disease, and studies to clarify the pathophysiological and prognostic value of these changes are needed.

Objetives: To assess blood pressure profile by ambulatory blood pressure monitoring (ABPM) in normotensive patients with acute Chagas disease (ACD) without apparent cardiac damage, and the influence of the infection on nocturnal blood pressure fall.

Methods: ABPM was performed with 54 patients with ACD and a control group composed of 54 age- and sex-matched normotensive individuals. The alpha level of significance (type I error rate) was set at 5%.

Results: In the total of 54 patients, 74.0% did not show nocturnal fall in systolic blood pressure, 53.7% did not show nocturnal fall in diastolic blood pressure, and lack of both nocturnal fall in SBP and DBP was observed in 51.8% (*p<0.05). In 12.9% of patients, there was an increase in SBP and in 18.5% increase in DBP (p<0.05).

Conclusions: In patients with acute Chagas disease, a significant absence of the physiological fall in both systolic and diastolic blood pressure was observed during sleep, and some of the patients showed nocturnal increase in these parameters. These findings suggest autonomic changes in the acute phase of Chagas disease. (Arq Bras Cardiol. 2020; 114(4):711-715)

Keywords: Chagas Disease/physiopathology; Blood Pressure/physiology; Autonomic Nervous System/physiology; Blood Pressure Monitoring, Ambulatory/methods; Hypertension.

Introduction

Chagas disease is a zoonosis caused by the flagellate protozoan *Trypanosoma cruzi* (*T. cruzi*) that feeds primarily on blood. The disease is endemic in 21 countries in Latin America, with an important social impact due to its high morbidity and mortality. According to the World Health Organization (WHO), it is estimated that 6-7 million people are infected, most of them in Latin America.[1] The classical form of transmission – vector transmission – has been decreasing in endemic areas in Latin America thanks to infection control initiatives. However, intense deforestation in the Amazon region, in addition to migration of people, has changed the epidemiological scenario, with an expressive increase in oral transmission.[2]

Mailing Address: Henrique Tria Bianco •
Universidade Federal de São Paulo – Escola Paulista de Medicina - Rua Loefgren, 1350 Postal Code 04040-001, São Paulo, SP – Brazil
E-mail: henriquetria@uol.com.br
Manuscript received February 26, 2019, revised mansucript June 09, 2020, accepted June 23, 2020

DOI: https://doi.org/10.36660/abc.20190143

The most common clinical presentation in the acute phase of the orally transmitted disease includes prolonged fever syndrome, usually associated with familial microepidemics, and several unspecific symptoms characteristic of vector transmission of Chagas disease, but with higher morbidity and mortality.[3-5] In the chronic form of the disease, important changes in the autonomic system are observed, with increased sympathetic activity and decreased parasympathetic activity. However, autonomic changes in the acute phase of the disease are not known so far. Many patients have altered blood pressure (BP) and abnormal ambulatory blood pressure monitoring (ABPM) measures, mainly related to nocturnal BP fall. In non-chagasic patients, such event has been regarded as a sign of dysautonomia and possible predictor of cardiovascular risk.[6] In light of the physiological decline in nocturnal BP, an ABPM in acute Chagas disease (ACD) is advisable, aiming at a better understanding of BP behavior, especially during sleep. Therefore, the aim of the present study was to assess BP behavior in patients with ACD using ABPM.

Methods

This was a single-center study conducted in a university hospital. ABPM was performed in 54 patients (convenience sample) with orally transmitted ACD, seen in an outpatient clinic of infectious and parasitic diseases and 54 age- and sex- matched healthy controls. This control group was used aiming at evaluating the prevalence of lack of nocturnal BP fall in individuals without comorbidities, since this variable has not been investigated in the Brazilian population. The healthy controls had no complaints or history of any disease, had a normal clinical examination and were not taking any medication at baseline. All participants or their legal representatives signed an informed consent form.

The ABPM was carried out using a Dyna-MAPA® device. Inclusion criteria were patients attending the outpatient clinic with a diagnosis of ACD confirmed by a positive parasitological and/or serological test, in addition to meeting the epidemiological criteria established by the Brazilian Ministry of Health's protocol, available at: http://portalms.saude.gov.br/saude-de-a-z/doenca-de-chagas. Exclusion criteria were presence of diabetes mellitus, neurological diseases, arterial hypertension, cardiovascular disease, ongoing infection, hematological disease such as anemia, conditions that may affect renal function, thyroid disease or other important systemic changes, use of illicit drugs, pregnancy and alcoholism.

In the control group, ABPM was performed with normotensive individuals. The test was ordered as a routine test (health check-up) rather than for suspected hypertension. Individuals with any type of cardiac disease were not included.

The following ABPM parameters were assessed: 24-hour systolic (SBP) and diastolic BP (SBP), BP during sleep and awake states, and BP fall during sleep. Physiological fall in SBP and DBP was considered as a reduction ≥ 10% in mean BP registered during sleep. The awake period was considered the period from 8 to 20 o'clock, whereas the sleep-period time from 20 to 8 o'clock on the day after, following the 2011 Brazilian Guidelines on ABPM and home blood pressure monitoring.[7]

The study was approved by the ethics committee of the Hospital Universitário João de Barros Barreto (CAAE 01278918.4.00000017).

Statistical analysis

The chi-square test was used to compare individuals that did not show a nocturnal BP fall between patients and control group. A $p<0.05$ was set as statistically significant. Categorical variables were presented as frequency, absolute numbers and percentage. Normally distributed variables were presented as mean and standard deviation. The Kolmogorov-Smirnov test and the histogram-normality test were used, and measurement of asymmetry and kurtosis was performed. The SPSS 23.0 software for Windows (IBM SPSS *Statistics* para Windows version 23.0, launched in 2015, Armonk, NY: IBM Corp).

Results

In the total of 54 patients with acute infection with *T. cruzi*, mean age was 36.2 ±10.4 years, 30 were women (mean age 34.7 ± 19.0 years) and 24 men (mean age 38.3 ± 19.7 years).

The ABPM showed that 40 patients (74.0%) did not show nocturnal fall in SBP, and 29 (53.7%) did not show nocturnal fall in DBP. This occurred concomitantly in 29 (53.7%) patients; seven (12.9%) showed nocturnal increase in SBP and 10 (18.5%) in DBP.

No statistically significant difference was found in the mean 24-hour SBP and mean 24-hour DBP during sleep and awake states between patients with ACD and control group (Table 1). Significant differences were found between the groups for nocturnal fall in SBP and DBP in both sexes.

Discussion

Discussion Changes in autonomic nervous system are well characterized in chronic Chagas disease, with neuron loss and lesion in the parasympathetic pathway and increased sympathetic activity. Studies on patients with the indeterminate form of Chagas disease have shown a predominance of parasympathetic activity in these patients, which was correlated with autonomic dysfunction.[9] Results of an interesting study indicated a relationship between changes in autonomic modulation and endothelial function in patients with ACD.[10] Lesions in the central nervous system were found in anatomopathological studies in ACD patients, described as distant systemic lesions caused by

Table 1 – Mean values of 24-hour blood pressure during sleep and awake states in 54 normotensive patients with acute Chagas disease and 54 normotensive individuals without Chagas disease (controls)

	Controls			Acute Chagas disease		
	24h	awake state	sleep	24h	awake state	sleep
Mean	114.1±10.3	117.3±10.4	100.9±10.0	111.0±10.6	112.7±10.5	105.1±11.7
SBP						
mmHg						
Mean	68.9±7.6	71.3±8.1	59.2±7.5	66.9±7.0	68.3±7.2	62.2±8.1
DBP						
mmHg						

Data expressed as mean and standard deviation; SBP: systolic blood pressure; DBP: diastolic blood pressure; ACD: acute Chagas disease

Table 2 – Number of patients with changes in ambulatory blood pressure monitoring (ABPM) in patients with acute Chagas disease and controls

	Controls			Acute Chagas disease		
	Women (n=30)	Men (n=24)	Total (n=54)	Women (n=30)	Men (n=24)	Total (n=54)
Absence of nocturnal fall in SBP	5	4	9 (16.6%)	20	20	40 (74.0%)*
Absence of nocturnal fall in DBP	4	3	7 (12.9%)	9	20	29 (53.7%)*
Absence of nocturnal fall in SBP and DBP	4	3	7 (12.9%)	16	12	28 (51.8%)*
Nocturnal increase in SBP	0	1	1 (1.8%)	5	2	7 (12.9%)*
Nocturnal increase in DBP	0	1	1 (1.8%)	5	5	10 (18.5%)*

Data expressed as absolute and relative numbers. Chi-square test for comparisons between acute Chagas disease and control groups; p<0.05.

ganglion cells.[11,12] Impairment of the nervous system can be demonstrated in all stages of Chagas disease, and changes in the parasympathetic autonomic nervous system control have not been correlated with cardiovascular symptoms by functional tests on humans.[13] The loss of autonomic control in chronic Chagas disease was described in a case-control study that evaluated the correlation between sympathetic innervation, changes in perfusion and abnormalities in the ventricular wall, showing that cardiac sympathetic dysfunction occurs in early stages of the disease and is associated with the worsening of autonomic dysfunction.[14] However, studies on autonomic function in the acute phase of Chagas disease are scarce. Evidences have shown the involvement of the autonomic nervous system, especially the parasympathetic system, soon after initial infection, i.e., in the undetermined phase of Chagas disease.[15]

Physiological variations in BP have a circadian rhythm, with fluctuations over 24 hours and BP drop during sleep. This fall, detected by ABPM, normally exceeds 10% of BP in the awake state, and is observed in approximately 95% of the normotensive individuals.[16] During sleep, there are specific changes in autonomic and endocrine functions, with reduced sympathetic activity and predominance of parasympathetic activity, leading to physiological BP fall.[17,18] The observations in clinical practice indicating that many patients with ACD that underwent ABPM for any reason did not show nocturnal fall of BP motivated the development of a systematic study to analyze the behavior of BP in ABPM. In the control group, we included only individuals with good cardiovascular health, with no history of hypertension, diabetes or cardiovascular disease. All individuals had normal office BP (mean of the last two measures <140/90 mmHg). The only drug taken by the patients with ACD was benznidazole, an antiparasitic medication used in the treatment of *T. cruzi* infection, the causative agent of Chagas disease. Lack of BP fall during sleep was seen in a large proportion (more than half) of patients with ACD, and nocturnal increase of BP occurred in a significant proportion of patients (12.9% in SBP and 18.5% in DPB).

The neurohumoral features of the acute phase of Chagas disease are not well known, mainly due to epidemiological characteristics and difficult diagnosis. However, due to changes in the disease profile and the increase in the number of cases of oral contamination, with greater parasite load, we have found more obvious clinical manifestations.[19] This lack of nocturnal fall in BP in the acute phase of Chagas disease may be the result of a disturbance in the autonomic nervous system. One limitation of this study is that we did not perform an analysis of heart rate variability, since our objective was to evaluate BP behavior over 24 hours.

Conclusions

The results of this study suggest that the ABPM can be a useful tool for early detection of autonomic changes in the acute phase of Chagas disease. Since this was a descriptive study of patients with ACD, it is not possible to understand the real meaning of these changes, since there is no consensus about the reproducibility of this result and clinical outcomes at long term.

Author contributions

Conception and design of the research and Acquisition of data: Souza DS, Oliveira CB, Maciel BG, Maciel MTS, Póvoa R; Analysis and interpretation of the data: Bianco HT, Póvoa R; Statistical analysis and Writing of the manuscript: Souza DS, Bianco HT, Póvoa R; Critical revision of the manuscript for intellectual content: Bianco HT, Fonseca FAH, Izar MC, Póvoa R.

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. WHO). Sustaining the drive to overcome the global impact of neglected tropical diseases: second WHO report in neglected tropical diseases. Geneva; 2013.
2. Dias JCP, Human Chagas Disease and Migration in the Context Of Globalization: some Particular Aspects. J Trop Med. 2013, ID 789758, 9 pages, doi 10.1155/2013/789758.
3. De Goes EC, Dos Santos SO, Sojo-Milano M, Amador EC, Tatto E, Souza DS, et a
1. World Health Organization.(l. Acute Chagas disease in the Brazilian Amazon: epidemiological and clinical features. Int J Cardiol. 2017, 235:176-8.
4. Pinto AY, Ferreira AG Jr, Valente V, Harada GS, Valente AS. Urban outbreak of acute Chagas disease in Amazon region of Brazil: four-year follow-up after treatment with benznidazole. Rev Panam Salud Publica, 2009, 25(1):77-83.
5. Barreto-de-Albuquerque J, Silva-dos-Santos D, Pérez AR, Berbere LR, Santana van Vilet E, Farias de Oliveira DA, Moreira OC, et al. Trypanosoma cruzi Infection through the oral route promotes a severe infection in mice: New disease form from an old infection? PLoS Negl Trop Dis. 2015; 9(6):e0003849.
6. Melo ROU, Toledo JCY, Loureiro AAC,Cipullo JP, Moreno Jr H, Martin JF. Absence of Nocturnal Dipping is Associated with Stroke and Myocardium Infarction. Arq Bras Cardiol. 2010; 94(1):74-80.
7. V Diretrizes Brasileiras de Monitorização Ambulatorial da Pressão Arterial (MAPA V) e III Diretrizes Brasileiras de Monitorização Residencial da Pressão Arterial (MRPA III). Sociedades Brasileiras de Cardiologia, Hipertensão e Nefrologia. Arq Bras Cardiol .2011; 97(3 Supl 3):1-24.
8. Correa-Araujo R, Oliveira JS, Cruz AR. Cardiac levels of norepinephrine, dopamine, serotonin and histamine in Chagas'disease. Int J Cardiol. 1991;31(3):329-36.
9. Rassi Jr A, Rassi A, Marin-Neto J. Chagas disease. Lancet. 2010; 375(9723):1388-402.
10. Truccolo AB, Dipp T, Eibel B, Ribeiro A, Casali KR, Irigoyen MC,et al. Associação entre Função Endotelial e a Modulação Autonômica em Pacientes com Doença de Chagas. Arq Bras Cardiol. 2013;100(2):135-40.
11. Oliveira NK, Ferreira RN, Lopes SDN, Chiari E, Camargos ERDS, Martinelli PM. Cardiac autonomic denervation and expression of neurotrophins (NGF and BDNF) and their receptors during experimental Chagas disease. Growth Factors. 2017;35(4-5):161-70.
12. E, Pérez AR, Pollachini N,Villar SR, Wildman J, Besedovsky H, et al. The sympathetic nervous system affects the susceptibility and course of Trypanosoma cruzi infection. Brain Behav Immun.2016 Nov;58:228-36.
13. Amorim DS, Godoy RA, Mango JC, Tanaka A, Gallo Jr L. Effects of acute elevation in blood pressure and of atropine on heart rate in Chagas' disease. A preliminary report. Circulation.1968; 38(2):289-94.
14. Simoes MV, Pintya AO, Bromberg-Marin G, Sarabanda A, Antioga CM, et al. Relation of regional sympathetic denervation and myocardial perfusion disturbance to wall motion impairment in chagas' cardiomyopathy. Am J Cardiol 2000;86(9):975-81.
15. Koberle F. Enteromegaly and cardiomegaly in Chagas disease. Gut 1963; 4(4):399-405.
16. Staessen JA, Bieniaszewski L, O'Brien E, Gosse P, Havashi H, Imai Y, et al. Nocturnal blood pressure fall on ambulatory monitoring in a large international database. The "Ad Hoc' Working Group. Hypertension .1997; 29(1Pt 1):30–9.
17. Murali NS, Svatikova A, Somers VK. Cardiovascular physiology and sleep. Front Biosci. 2003 June; 8:S636-S652.
18. Dodt C, Breckling U, Derad I, Plasma epinephrine and norepinephrine concentrations of healthy humans associated with nighttime sleep and morning arousal. Hypertension. 1997;30(1):71-6.
19. Souza DSM , Póvoa RMS. Aspectos epidemiológicos e clínicos da doença de Chagas aguda no Brasil e na América Latina. Rev Soc Cardiol Estado de São Paulo. 2016;26(4):222-9.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Nocturnal Blood Pressure Dipping and the Autonomic Nervous System

Fernando Antonio de Almeida

Departamento de Clínica da Faculdade de Ciências Médicas e da Saúde da PUC-SP, campus Sorocaba, Sorocaba, SP – Brazil

Short Editorial related to the article: Absence of Nocturnal Fall in Blood Pressure Detected by Ambulatory Blood Pressure Monitoring in Acute Chagas Disease Patients with Oral Infection

Blood Pressure (BP) is continuously controlled by complex mechanisms involving the structural characteristics of the arterial system, the autonomic nervous system (sympathetic and parasympathetic) integrated with the baroreceptor and chemoreceptor systems, the circulating volume and several vasoconstrictor and vasodilator hormone systems with systemic and local actions.[1] The integration of these systems ensures that the blood pressure undergoes minimal variations in small intervals, but if we consider the whole day, there are times, such as during sleep and when getting up in the morning, when there are more intense variations in blood pressure, always around mean values. Ambulatory blood pressure monitoring (ABPM) allows this phenomenon to be recorded in clinical practice.

Figure 1 shows the ABPM graphical record of a person with arterial hypertension, indicating the main parameters evaluated in this exam. One of the most important phenomena that can be assessed by ABPM is the physiological BP dipping during sleep. This physiological behavior of BP during sleep occurs because many vasoconstrictor mechanisms are "disarmed" in this condition; among them, the autonomic nervous system is one of the most important.[2] A direct consequence of this modulatory effect of the autonomic nervous system is that, in diseases or clinical conditions in which the system is affected, the absence of this modulatory effect is expressed by the absence of BP dipping during sleep. In some cases, there may even be an increase in BP during sleep. This is the classic example of individuals with diabetes mellitus with autonomic neuropathy.[3-5] These individuals frequently have postural hypotension, elevated BP at bedtime and absence of BP dipping during sleep.[3,4,6,7] The absence of BP dipping during sleep implies a higher pressure load on the circulatory system and increases the risk of cardiovascular events in the long-term.[8,9] There are other clinical conditions associated with the absence of BP dipping during sleep, but this is not the case of this discussion.

In the original article published in this issue of *Arquivos Brasileiros de Cardiologia,*[10] using the case-control study as a methodological strategy, the authors documented by ABPM that 54 adults (30 women, mean age 36 years) with acute Chagas disease transmitted orally have a higher prevalence of the absence of BP dipping during sleep (74%) and higher prevalence of BP increase during sleep (18.5%). The frequency with which these changes occur in the study participants with acute Chagas' disease was significantly higher when compared to participants in the control group, respectively 16.6% and 1.8%. The increase in BP during sleep is also a characteristic of patients with diabetes mellitus.[7]

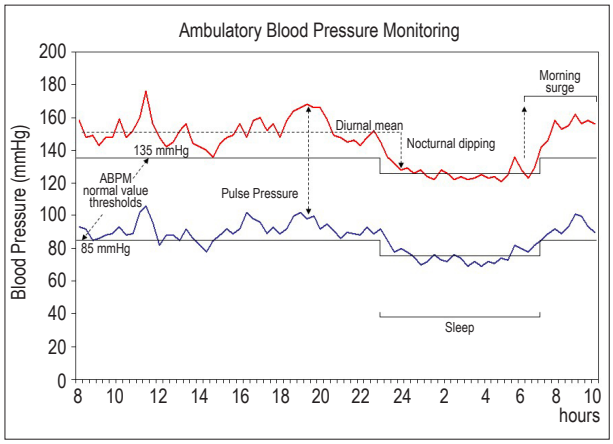


Figure 1 – *Graphical record of an ambulatorial blood pressure monitoring of a person with hypertension. Observe nocturnal dipping and morning surge.*

The authors identified that these alterations occur early in acute Chagas' disease and interpreted that such alterations in ABPM may result from dysautonomia, a characteristic of chronic Chagas' disease, which is already present in the acute phase of the disease. The study is an important contribution to the knowledge in the area, as it produces a remarkable documentation of functional alterations in the autonomic nervous system in the early stages of Chagas' disease.[10] A question that immediately arises is whether the treatment of Chagas' disease in the acute phase can prevent the progression of or recover the already established neurological lesions. The latest Brazilian guideline on Chagas' disease mentions the absence of parasitemia and the reduction in antibody titers over 5 to 10 years as the cure criteria but does not address this aspect of the disease.[11] The authors of the present study have the opportunity to monitor these patients for prolonged periods of time to assess whether the treatment of acute Chagas' disease can modify the evolution of the autonomic nervous system lesions.

Keywords

Chagas Disease; Autonomic Nervous System; Blood Pressure Monitoring Ambulatory; Blood Pressure; Sleep; Diabetes Mellitus

Mailing Addres: Fernando Antonio de Almeida •
Rua Joubert Wey 290. Postal Code 18030-070, Sorocaba, SP – Brazil
E-mail: almeidafa@globo.com

DOI: https://doi.org/10.36660/abc.20200280

References

1. Almeida FA, Rodrigues CIS. Hipertensão arterial primária. In: Riella MC, Princípios de nefrologia e distúrbios hidroeletrolíticos. 6. ed. Rio de Janeiro: Guanabara Koogan; 2018. p. 605-37.
2. Mancia G. Autonomic Modulation of the Cardiovascular System during Sleep. N Engl J Med. 1993;328(5):347-9.
3. Cardoso CRL, Leite NC, Freitas L , Dias SB, Muxfeld ES, Salles GF. Pattern of 24-hour ambulatory blood pressure monitoring in type 2 diabetic patients with cardiovascular dysautonomy. Hypertens Res. 2008; 31(5):865-72. DOI:10.1291/hypres.31.865
4. Hjortkjær HØ, Jensen T, Kofoed KF et al. Nocturnal antihypertensive treatment in patients with type 1 diabetes with autonomic neuropathy and non-dipping: a randomised, placebo-controlled, double-blind cross-over trial. BMJ Open. 2016; 6(12):e012307. DOI:10.1136/bmjopen-2016-012307
5. Najafi MT, Khaloo P, Alemi H, Jaafarinia M, Mirboulok M, Mansournia MA, et al. et al. Ambulatory blood pressure monitoring and diabetes complications: Targeting morning blood pressure surge and nocturnal dipping. Medicine (Baltimore). 2018;97(38):e1218
6. Vinik AI, Ziegler D. Diabetic Cardiovascular Autonomic Neuropathy. Circulation.2007;115(3):387-97.
7. Sun L, Yan B, Gao Y,Su D, Peng L, Jiao Y, et al. Relationship between blood pressure reverse dipping and type 2 diabetes in hypertensive patients. Sci Rep. 2016 Apr 25;6:25053.
8. Ohkubo T, Hozawa A, Yamaguchi J,Kikuya M, Ohmori K, Michimata M, et al. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. J Hypertens. 2002;20(11):2183-9.
9. Cuspidi C, Giudici V, Negri F, Sala C. et al. Nocturnal nondipping and left ventricular hypertrophy in hypertension: an updated review. Expert Rev Cardiovasc Ther. 2010;8(6):781-92.
10. Souza DSM, Oliveira CB, Maciel BG, Figueiredo MT, Bianco HT, Fonseca FAH, et al. Absence of Nocturnal Fall in Blood Pressure Detected by Ambulatory Blood Pressure Monitoring in Acute Chagas Disease Patients with Oral Infection. Arq Bras Cardiol. 2020; 114(4):711-715.
11. Dias JCP, Ramos Jr NA, Gontijo ED, Luquetti A, Shikanai-Yasuda MA, Coura JR, et al. II Consenso Brasileiro em Doença de Chagas, 2015. Epidemiol Serv Saude. 2016;25(n.especial):7-86.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Artificial Intelligence in Cardiology: Concepts, Tools and Challenges - "The Horse is the One Who Runs, You Must Be the Jockey"

Erito Marques de Souza Filho,[1,2] Fernando de Amorim Fernandes,[1] Celine Lacerda de Abreu Soares,[1] Flavio Luiz Seixas,[1] Alair Augusto Sarmet M.D. dos Santos,[1] Ronaldo Altenburg Gismondi,[1] Evandro Tinoco Mesquita,[1] Claudio Tinoco Mesquita[1]

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

Universidade Federal Rural do Rio de Janeiro - Departamento de Tecnologias e Linguagens,[2] Nova Iguaçu, RJ – Brazil

Abstract

The recent advances at hardware level and the increasing requirement of personalization of care associated with the urgent needs of value creation for the patients has helped Artificial Intelligence (AI) to promote a significant paradigm shift in the most diverse areas of medical knowledge, particularly in Cardiology, for its ability to support decision-making and improve diagnostic and prognostic performance. In this context, the present work does a non-systematic review of the main papers published on AI in Cardiology, focusing on its main applications, potential impacts and challenges.

Introduction

A person's everyday life necessitates a huge amount of knowledge about the world and the volume of data in health grows exponentially throughout the world.[1] On the other hand, biomedical knowledge is always expanding in an active and dynamic way and cannot be processed or stored by a single human brain. This situation makes it very difficult for the contemporary physician to keep up-to-date with such a broad spectrum of new data and findings, as well as to use such information easily and in a timely manner.[2] Adding to this framework are the significant burnout rates among health professionals[3,4] and the important impact of medical errors - which in the United States represent the third leading cause of death.[5] This panorama brings with it the need to reorganize the productive structure of health services, associated with various challenges and new perspectives. Given that the current health system is generally unproductive and/or expensive, it is imperative to develop alternative and innovative strategies. The central focus for achieving this goal should be to increase the value for the patient – outcomes reached per dollar spent – so that good outcomes, efficiently obtained, are a target to be pursued.[6]

Besides, the recent advances at hardware level related to parallel processing, the existence of several machine-learning methods and the huge amount of annotated data contributed for artificial intelligence (AI) to promote a significant paradigm shift in the most diverse areas of medical knowledge and, particularly in Cardiology, for its ability to support decision-making that can improve diagnostic and prognostic performance. These impacts ought to be evaluated from the perspective of patient safety, personalization of care, value creation for the patients, within a scope of technological surveillance – that gradually consolidates AI as fundamental for a medical practice of excellence.[7-11]

This scenario makes AI, given its importance, be considered by many as the new electricity. The main journals in cardiology have published reviews in this area and the number of articles on the subject follows a growing trend, as shown in Figure 1 – this behavior is also seen in other medical specialties, such as Neurology. Therefore, the present work performs a non-systematic review of the main papers published on AI in Cardiology, focusing on its main applications, potential impacts and challenges. The next section presents the conceptual fundamentals on the topic, followed by a discussion on why cardiology needs AI and its main tools. Finally, the main challenges, perspectives and conclusions are presented.

What is artificial intelligence?

The term AI was used for the first time at the Dartmouth Conference in 1956.[12] Nevertheless, the possibility of machines being able to simulate human behavior and actually think was raised earlier by Alan Turing in 1950, who developed a test in order to differentiate humans from machines – thus named Turing test.[13]

Basically, AI is the product of the combination of sophisticated mathematical models and computation, which allows the development of complex algorithms capable of emulating human intelligence. All this process starts with the construction of a database representative of the problem that one wishes to study – adequately collected and processed– called healthy data. This step is of fundamental importance, as the algorithms will probably not perform well if this prerequisite is not obtained: "*garbage in, garbage out*".

The nature of these data is quite varied, ranging from socio-environmental, clinical-laboratory, omic-data (e.g., metabolome, proteome, epigenome, lipidome) to information on red, green and blue intensities (RGB system) of each pixel that composes an image, for example. Equally diversified sources of such data include those obtained from electronic medical records or even wearable devices. In this context, the term Big Data is used to describe a huge collection of data for which traditional methods of analysis are unsuccessful in analyzing, searching, interpreting and storing.[9]

We highlight the use of these tools in problems of classification, regression, and clusterization. After obtaining

Keywords

Artificial Intelligence/trends; Computer Systems/trends; Machine Learning/trends; Cardiovascular Diseases; Clinical Decision-Making.

Mailing Address: Erito Marques de Souza Filho •
Universidade Federal Fluminense - Departamento de Medicina Clínica – Av. Marques do Paraná, 303. Postal Code 24033-900, Niterói, RJ – Brazil
E-mail: mederitomarques@gmail.com
Manuscript received December 21, 2018, revised manuscript July 16, 2019, accepted August 28, 2019

DOI: https://doi.org/10.36660/abc.20180431

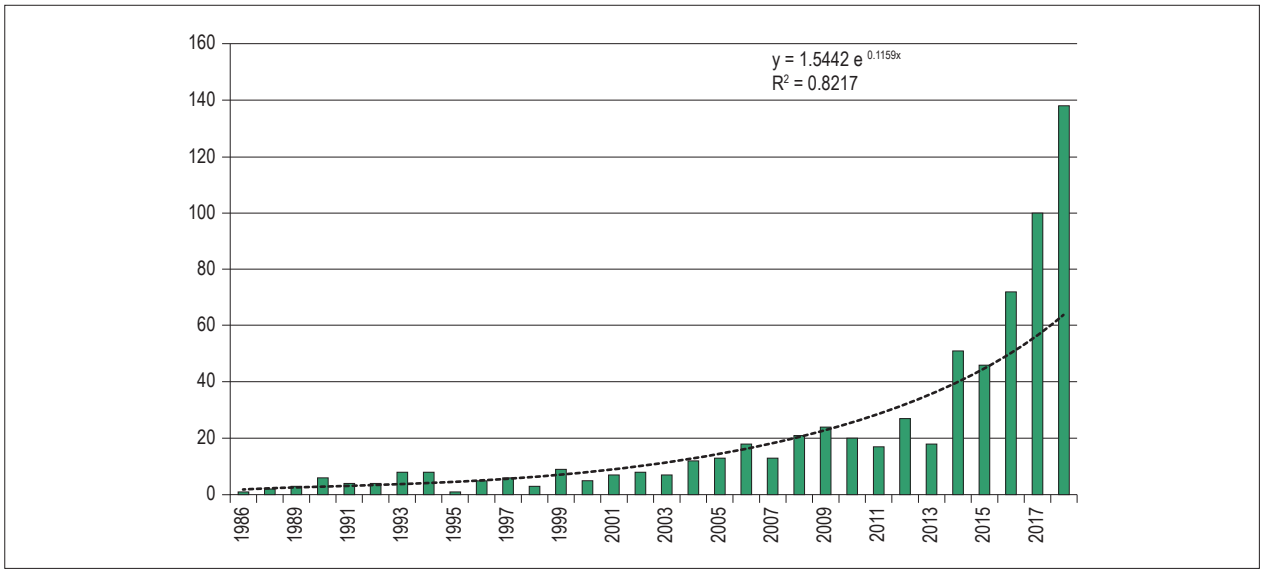


Figure 1 – *Evolution of the number of works relating (Artificial Intelligence or Machine Learning) and Cardiology. Source: Pubmed. Accessed on 12/15/2018. Mesh Words: Cardiology and Machine Learning.*

healthy data and building the database, it is important to evaluate which mathematical models of AI are most appropriate for the problem that one wishes to solve. Then, the chosen models must be implemented using some programming language. A combination of models can also be useful. The results obtained by the algorithm should be analyzed in terms of both the coherence and suitability. These steps are summarized in Figure 2.

Why does cardiology need artificial intelligence?

The development of AI algorithms has the advantage of not requiring many assumptions in relation to underlying data.[8] Another point is that the nature of these mathematical-computational models allows, from observational data, a high level of evidence due to its high performance, which certainly represents a significant paradigm shift in evidence-based medicine. It should be noted that traditional clinical trials are generally slow, expensive, time-consuming, and limited in size.[14] In addition, when the database is fed with more (healthy) data, in general, there is an improvement in the performance of the algorithms – which allows the studies to have a continuous character over time.

This new archetype can guide the allocation of scarce resources in the health area and facilitate the efficient and accurate identification of decisions that favor the individualization of care based on the flow of information that emerge from an integrated and complex ecosystem: it is a precision medicine.[15,16] Therefore, it can be inferred that the practice of the cardiovascular sciences will have significant impacts, which will translate into a personalized approach and improved outcomes.

Basic concepts in artificial intelligence

A generic database can be arranged in a matrix of rows and columns. Each line denotes an element from a set of objects to be evaluated according to the same features. Each column, in turn, expresses the values of a given attribute for the various rows in the database and each line represents a lesson to be learned by the mathematical-computational model. In this way, the term Machine Learning (ML) brings with it a possibility of "*learning*" from a set of lessons. The term AI is often used interchangeably with the term ML. However, ML is a subset of AI algorithms related the ability of learn from a large amount of data. AI is wider and encompass performing tasks that are normally related to human intelligence such as pattern recognition, problem solving, understanding language or recognizing objects and sounds.[17]

It is often said that the types of learning can be:

a) Supervised: when the algorithm receives information about each lesson as well as the labels associated with it, having an important role in relation to the prediction. For example, if it is desired to predict whether a patient is more susceptible to cough with the use of angiotensin-converting enzyme inhibitors, analysis should be performed based on a healthy database containing a group of patients that showed such a reaction and another group in which this fact was not observed.

b) Unsupervised: when the lesson labels are not provided *a priori*, it is up to the algorithm to find hidden structures in the database. A hypothetical example is the clusterization of a database of patients with hypertrophic cardiomyopathy according to imaging findings.

c) Reinforcement: inspired by behavioral biology, it is a kind of reward-based learning.[18,19]

Another important concept is that of cognitive computing. It can be understood as a set of self-learning systems intended to imitate the human thought process based on the use of ML tools, pattern recognition and natural language processing.[9] IBM Watson is an example of cognitive computing in the medical field.[20,21]

Some artificial intelligence tools and applications

Currently, there is a multiplicity of models of ML each of them with diverse particularities, varied uses and limitations. The applications of some of these models in Cardiology are explained in the following paragraphs, while a brief description of each of them and their type is shown in Table 1.

a) Support Vector Machine (SVM): used by Samad et al.,[22] to predict with success the deterioration of ventricular function in patients with repaired tetralogy of Fallot from a database of 153 patients with clinical, electrocardiographic and cardiac magnetic resonance imaging data. In relation to predicting any deterioration (minor or major) vs. no deterioration, the mean area under the curve (AUC) was 0.82 ± 0.06.[22] Berikol et al.[23] used clinical, laboratory (troponin I and CK-MB levels), ECG, and echocardiographic data from 228 patients who presented at the emergency department with chest pain for classification regarding the presence or absence of Acute Coronary Syndrome. Accuracy, sensitivity and specificity were, respectively, 99.19, 98.22 and 100%.[23] Betancur et al.[24] also used SVM to more precisely define mitral valve plane (VP) positioning during left ventricular segmentation in Single-Photon Emission Computed Tomography (SPECT) exams. Images of 392 patients were analyzed and the good results obtained were compatible with the opinion of experts in the area – AUC: 0.82 [0.74-0.9] for regional detection of obstructive stenosis and ischemic total perfusion deficit areas.[24]

b) Naive Bayes (NB): Paredes et al.,[25] used an NB fusion and genetic algorithm to predict the risk of occurrence of cardiovascular events (e.g., hospitalization or death) based on data from 559 Acute Coronary Syndrome-Non-ST Segment Myocardial Infarction (ACS-NSTEMI) patients. Sensitivity and specificity were, respectively, 79.8, 83.8.[25]

c) K-nearest neighbors (KNN): Al-Mallah et al.[26] compared the prediction of all-cause mortality in 10 years between the classical logistic regression model and the KNN, considering a database of 34,212 patients with clinical information and information obtained after the treadmill test using the standard protocol of Bruce.[26] The results obtained by this ML tool showed a sensitivity of 87.4% and specificity of 97.2%, better than the predictive performance of the traditional Atherosclerosis Cardiovascular Disease Risk Score (ASCVD).

d) Genetic algorithms (GA): Smisek et al.[27] developed a wearable device to detect arrhythmias from the information record of a single-lead electrocardiogram. The data were analyzed from a combination of the (SVM), decision tree and

Table 1 – Brief description and classification of the main ML tools

Tool	Description	Learning
SVM	It is useful for two-group classification problems. The idea is to find a function called hyperplane from the resolution of a linear system built from the various lessons of the training subset.[40] This hyperplane is used to cluster the lessons of the test subset into two disjoint groups.	Supervised
NB	It was inspired in the studies of the reverend Bayes on conditional probability.[41] These probabilities are used to identify the category (out of a total n possible) that a particular lesson belongs to.[42]	Supervised
KNN	It is said that a vector norm is a mathematical function, which satisfies specific properties, and associates a vector with a value greater than or equal to zero.[43] The norm of the difference between two vectors is the distance between them. The KNN uses a norm to calculate the distance between all the vectors (lessons) that make up the database. Then, for each vector of the database, the k vectors closest to it are determined. The inclusion in a given group is obtained from a majority voting system among the neighbors.[44,45]	Supervised
AG	Algorithms inspired by the biological evolution of species, in which each possible candidate to solve the problem is modeled as a chromosome consisting of a set of genes, which during the execution of the algorithm undergoes operations of crossing-over and mutation in order to obtain better solutions than the current ones.[46] This way, they allow a database to be separated, for example, into two distinct groups – which have or do not have a particular characteristic.	Supervised
RF	This method is based on the construction of several decision trees. The first step is to get several random samples (with reposition) of lessons to build other databases, a process that is called bootstrapping. Each of these new databases will give rise to a decision tree, which is obtained iteratively, from a subset of variables (features). After the construction of all trees, a new lesson in the database should be allocated to the group that has the largest number of decision trees, showing that it belongs to this group (majority of votes).[47,48]	Supervised
K-means	It allows partitioning a database into k groups with similar characteristics. To do so, it is necessary to update, in an iterative way, a set of vectors, called reference centroids of each group and to calculate the distance of each lesson to each one. A lesson is always allocated to the centroid for which it has the shortest distance. The elbow chart is generally used to determine the ideal number of groups to separate from the database.[49]	Unsupervised
ANN	Inspired in biological nerve systems, a structure called a graph - a set of nodes and edges - is used in which nodes are layered and connected by valued edges, which represent a weight assigned to a given connection. The idea is that from a set of inputs, these weights are used properly to produce an output. Several architectures have been proposed for neural networks, from simpler ones such as the perceptron, to more sophisticated ones, such as the radial basis function, convolutional networks and deep learning. In deep learning, in addition to the input and output layers, there are hidden layers that increase significantly the number of weights to be updated and often require huge computational efforts. Convolutional network is a type of deep leaning inspired in visual cortex of animals that have an important role in image analysis. Autoencoders and Kohonen neural networks are examples of unsupervised learning.[1,7,50-52]	Unsupervised or Supervised
GB	It is a tree-based method that uses gradient, vectors related to the direction of maximum increase in a math function, to produce sequential decision trees to be combined to brush up on the prediction. Variants of this approach include Stochastic Gradient Descent that incorporates a random subsampling to GB.[53,54]	Supervised

threshold-based rules. Genetic algorithms were used to select the most appropriate characteristics to be used in the work. In relation to the detection of atrial fibrillation, an F1 score (harmonic mean of positive predictive value and sensitivity) of 0.81 was obtained.[27] Stuckey et al.,[28] used the Cardiac Phase Space Tomography Analysis - a pioneering method that dispenses with the use of radiation and contrast, as well as performing exercises or pharmacological stress - combined with ML models (e.g., genetic algorithms) to analyze the thoracic phase signals. In this study, the authors used this tool to evaluate patients with coronary disease and chest pain who were referred by the physician for angiography. 606 patients were studied, and the results showed sensitivity of 92%, specificity of 62% and predictive value of 96% for coronary disease.[28]

e) Random Forests (RF): Samad et al.,[29] analyzed a database consisting of clinical and electrocardiographic variables to evaluate survival in 10 different periods of time (ranging from 6 to 60 months), considering a total of 171,510 patients. RF was used, with excellent results, better than those obtained through traditional scores such as the Framingham risk score and ACC/AHA guideline score. The area under the curve (AUC) was superior to 0.82.[29] Ambale-Venkatesh et al.[30] used information from noninvasive tests, questionnaires, biomarkers and imaging tests from 6,814 patients to construct 739 variables (features) in order to apply a variant of RF – called survivor random forests[31] – for predicting cardiovascular events (all-cause death, stroke, all cardiovascular disease, coronary heart disease, atrial fibrillation and heart failure), having performed better than established risk scores, e.g., MESA-CHD, AHA/ASCVD and Framingham, with increased prediction accuracy (decreased Brier score by 10%-25%).[30,31]

f) K-means: Cikes et al.[32] used a database consisting of clinical variables and echocardiographic parameters for which two models of ML, Kmeans and Multiple Kernel Learning were applied, in order to categorize the patients into mutually exclusive groups to evaluate the response to resynchronization therapy cardiac. A total of 1,106 patients were analyzed and four disjoint groups were identified, two of them with the best response to therapy.[32]

g) Artificial Neural Networks (ANN): Kwon et al.,[33] in a multicenter study of 52,131 patients, constructed a deep learning-based early warning system capable of predicting the occurrence of cardiac arrest in a hospital. The model showed high performance when compared to traditional track-and-trigger systems. The area under the curve was 0.82.[33] Rubin et al.,[34] had promising preliminary results with the use of neural networks with convolutional architecture to evaluate electrocardiographic signs and to classify them in atrial fibrillation, sinus rhythm (normal) or noise – the F1 score achieved was 0.82.[34] Zhang et al.[35] also used convolutional neural networks to analyze a database with 14,035 echocardiographic exams to detect the presence of diseases such as hypertrophic cardiomyopathy, cardiac amyloidosis and pulmonary arterial hypertension with a high performance: C statistics were respectively, 0.93, 0.87, and 0.85.[35] Nakajima et al.[36] used an ANN to evaluate the presence of coronary disease after performing myocardial scintigraphy. Results were obtained with high accuracy and superior performance to the traditional scores used. For example, the AUC for patients with old myocardial infarction based on defects in rest stage was 0.97.[36]

h) Gradient Boosting (GB): Mortazavi et al.[37] used GB for prediction of risk of bleeding after percutaneous coronary intervention and demonstrated that these tools can help to identify patients who would benefit from strategies aiming to reduce the bleeding risk. A total of 3,316,465 procedures were analyzed and a C statistic of 0.82 was obtained.[37] Hernesniemi et al.,[38] also proposed a GB to predict mortality in acute coronary syndrome, analyzing 9,066 consecutive patients. The AUC was 0.89 and the model performed better than GRACE traditional score.[38]

It is important to note that when using any ML model, one should keep in mind a major problem that may arise, called overfitting. It occurs when a model describes the examples very well (training subset) and performs poorly when applied to other instances of the same phenomenon.[39] In addition, it is worth saying that there is no theoretical result that ensures that any of the AI algorithms is better than the others in any application. Thus, this choice depends on several variables, such as the nature of the problem under analysis, the time and resources available to solve the problem. The combination of techniques generating hybrid models can also be of great value. On the other hand, the use of tools for parallel processing, such as the Graphic Processing Unit (GPU), has been of great value in improving the performance of ML models, especially in relation to computational time needed to run them.

Challenges and future prospects

As previously highlighted, AI applications in cardiology have increased greatly in recent years and their growth potential is enormous. However, this scenario brings with it the need to overcome some challenges, such as: ethical limits of use (misuse), improvement of mathematical knowledge, acquisition of healthy data, development of security, need for collaboration, attention to errors and data-based care. All of this is discussed below and is summarized in Figure 2.

a) Challenge 1 – ethical limits of use (misuse): like all disruptive technology, the limits of ethics need to be rethought and widely discussed. ML algorithms can be misused and misleading. As an example, a work of great repercussion was published by Wang and Kosinski (2018). The authors used deep learning and obtained expressive results in the prediction of whether an individual is gay or not from a database of images of the study participants' faces.[55] Similarly, the same AI algorithms can be used to detect, for example, whether or not a patient will develop atrial fibrillation or any future cardiomyopathy. Could this information be used by companies to increase the amounts of their health plans or even deny membership to the plan due to a high cost? What if it is detected that a baby will be born with congenital heart disease due to the analysis of the genetic, clinical-laboratory and image (or other) data of its parents? This could open space for a kind of neoeugenia. This debate has gained an additional emphasis with the emergence of the CRISP-Cas9 technique, which allows DNA editing.[56] In this context, by stimulating a debate with society on the subject, transparency and regulation are fundamental pillars to be preserved.

b) Challenge 2 – improve math knowledge: the advent of this new kind of unbelievable human being (*Homo incredibile*), which supports its decisions in data, carries with

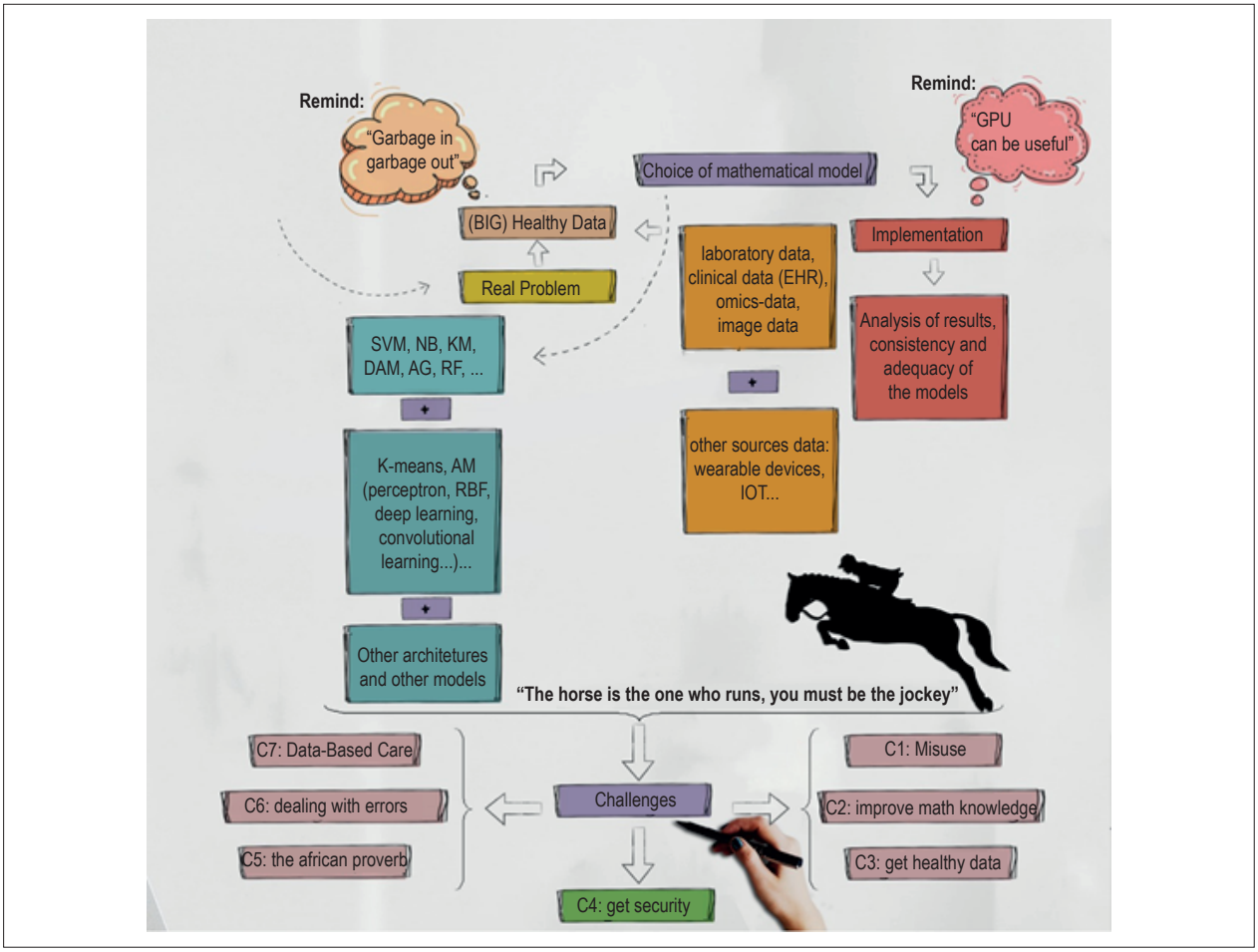


Figure 2 – *Main Illustration.*

it the fundamental role of mathematics and computation in this currently ongoing revolution. This revolution will bring unimaginable possibilities in medical practice, such as the construction of quality phenomappings - ML models developed with the aim of clustering patients in function of their large mass of phenotypic characteristics in order to facilitate the decision-making process.[57] Thus, it is necessary that these competencies are stimulated early, mainly with a focus on solving problems related to the reality for which one wishes to promote improvements. This will certainly be reflected in a need to reformulate the cardiovascular contents (and why not say, medical content in general) of undergraduate and postgraduate courses in Medicine: a passive or merely expositive education, with an extensive load and that prioritizes the capacity of the student's memory seems, more and more, to be inadequate, as one realizes that Medicine must be a space for creativity and value generation.

c) Challenge 3 – get healthy data: the use of healthy data is of fundamental value for the success of the algorithms. Thus, it is required that health units encourage their health professionals regarding the thoroughness at the level of data filling/obtaining as well as maintaining any data sources, from forms, electronic medical records, image data or even unconventional data, such as those obtained by Medina et al.[58] - who developed a successful Online Social Networks Health tool in which the patient himself anonymously inserts health monitoring information, including physiological data, daily activities, emotional states, and interaction with others patients.[58] Therefore, data management becomes as important as other routine behaviors in evidence-based medicine, such as proper handwashing or even the use of a defibrillator during cardiac arrest. In this way, the formation of multidisciplinary data teams and the constant training of the teams assume a primordial role. It is noteworthy that much of the slowness and difficulty that some health units have in using ML models is tied to absent or incipient healthy data.

d) Challenge 4 – get security: the advent of these tools brings with it a fundamental concern with data security, to a level never before experienced, as access to such data by unauthorized persons can lead to catastrophic consequences for both health institutions and the patients. The creation of a security team plays an important role in this new process. The General Data Protection Regulation represents an advance in this direction. Blockchain and its variants are important tools that can improve security substantially.

e) Challenge 5 – need for collaboration (the African proverb): there is an African proverb that says, "*if you want to go fast go by yourself, but if you want to go far go with many*". This applies a lot to this data environment: collaboration between institutions allows the construction of huge healthy databases (Big Data), which tends to favor the performance of ML algorithms.

f) Challenge 6 – dealing with errors: one important issue concerns the errors of AI models. It is inadequate to believe that such models are error-free. It may, for example, be the result of overfitting or occurring by using unhealthy data - which make the results unreliable. However, the practice has shown high performance in several applications. These models are probabilistic, and it is always desirable that their errors be minimal. This scenario has clinical implications, for example, an AI model that predicts with 99% probability that a patient has a greater propensity than the general population to have cardiac myocarditis or amyloidosis. There is a probability, although small, that this will not occur, and that the procedure adopted by the cardiologist is inadequate. In that case, the question is who can be held accountable in these cases? Is it appropriate? Should the patient sign a consent form in these cases? Certainly, the solution includes robust regulation of the use of these tools and strengthening of a new type of relationship: physician-patient-data.

g) Challenge 7 – data-based care management: while ML's tools follow an inexorable path, on the other hand, several healthcare professionals remain fearful about these tools because of its possible ability to replace physicians in their tasks. However, when the history of Medicine is remembered, it is worth mentioning, for example, that the appearance of automated machines to perform the whole blood count did not replace the hematologist, but rather resulted in a greater speed of the work process and allowed the professional to be able to act in other important issues in the specialty.

The central idea is to provide better support for decision-making, including better performance. It is data-driven care management with a high dynamism and constant updating - which will promote greater personalization of care[59] and a real-time evaluation of the experience of the health system users, aiming at generating value for the patient. In this context, the mechanical tasks will be substitutable and a diversity of new tasks will be included into the routine of the cardiologist of precision, from the adequate construction of the databases to the critical reflection on the results obtained by the mathematical-computational models, as well as the development of an adequate physician-patient-data relationship. Therefore, there is a migration of human skills as well as the expansion of their capabilities from the emergence of new tools, which should be part of the technical arsenal of the 21st century cardiologist. This panorama allows us to compare ML models to a horse and doctors to jockeys: " *the horse is the one who runs , you must be the jockey*".

Conclusions

AI, in fact, has been shown to be a fundamental tool for the clinical practice of current cardiology. Several applications have been successfully performed and have allowed significant improvements from a diagnostic and therapeutic point of view and in relation to personalized care. To be able to use such tools, it is imperative that healthy data be used, which certainly implies a new design in the modus operandi of many health services. The nature of these data is varied and includes new sources, such as wearable devices and omic-data. On the other hand, this new digital ecosystem requires an acquisition of knowledge not traditionally found in regular medical courses. Therefore, a curricular redesign is required and ought to be object of a profound debate and specific actions.

On the other hand, the entire panacea brought by AI is not free from challenges such as: the ethics limits of its use, the necessity of improving math knowledge, the building of an ecosystem that ensure high levels of security and confidentiality for the patients, the acquisition of healthy data, the needs of expand the physician-patient-data association, the necessity of collaboration and the data-based care management. In this context, the cardiologist-jockey (or physicians in general) must be a protagonist of changes and has to replace an eventual fear of the tools by a greater involvement with the objective of generating value for the care. It is important to keep in mind possible challenges and obstacles to be overcome and to maintain an engagement and critical sense in the search for solutions: "the horse is the one who runs, you must be the jockey".

Author contributions

Conception and design of the research: Souza Filho EM, Seixas FL, Santos AASMD, Gismondi RA, Mesquita ET, Mesquita CT; Acquisition of data: Souza Filho EM, Fernandes FA, Soares CLA, Santos AASMD; Analysis and interpretation of the data: Souza Filho EM, Fernandes FA, Soares CLA, Seixas FL, Gismondi RA, Mesquita ET, Mesquita CT; Writing of the manuscript: Souza Filho EM, Fernandes FA, Soares CLA, Gismondi RA, Mesquita ET; Critical revision of the manuscript for intellectual content: Seixas FL, Santos AASMD, Mesquita CT.

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 Doctoral submitted by Erito Marques de Souza Filho, from Universidade Federal Fluminense.

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. Goodfellow I, Bengio Y, Courville A. Deep Learning. Cambridge: MIT Press; 2016.
2. Dilsizian SE, Siegel, EL. Artificial intelligence in medicine and cardiac imaging: harnessing big data and advanced computing to provide personalized medical diagnosis and treatment. Curr Cardiol Rep. 2014;16(1):441.
3. Michel JB, Sangha DM, Erwin JP 3rd. Burnout among cardiologists. Am J Cardiol. 2017;119(6):938-40.
4. Rotenstein LS, Torre M, Ramos MA, Rosales RC, Guille C, Sen S, et al. Prevalence of burnout among physicians: a systematic review. JAMA. 2018;320(11):1131-50.
5. Macary MA, Daniel M. Medical error – the third leading cause of death in the US. BMJ. 2016 May 3;353:i2139.
6. Porter ME. A strategy for health care reform – toward a value-based system. N Engl J Med. 2009;361(2):109-12.
7. Dilsizian ME, Siegel EL. Machine meets biology: a primer on artificial intelligence in cardiology and cardiac imaging. Curr Cardiol Rep. 2018;20(12):139.
8. Johnson KW, Soto JT, Glicksberg BS, Shameer K, Miotto R, Ali M, et al. Artificial Intelligence in Cardiology. J Am Coll Cardiol. 2018;71(23):2668-79.
9. Krittanawong C, Zhang H, Wang Z, Aydar M, Kitai T. Artificial intelligence in precision cardiovascular medicine. J Am Coll Cardiol. 2017;69(21):2657-64.
10. Massalha S, Clarkin O, Thornhill R, Wells G, Chow BJW. Decision support tools, systems, and artificial intelligence in cardiac imaging. Can J Cardiol. 2018;34(7):827-38.
11. Mesquita CT. Artificial intelligence and machine learning in cardiology – a change of paradigm. Int. J. Cardiovasc. Sci. 2017;30(3):187-8.
12. Moore J. The Dartmouth College Artificial Intelligence Conference: The Next Fifty Years. AI Magazine. 2006;27(4):87-91.
13. Turing AM. Computing machinery and intelligence. Mind. 1950;59(236):433-60.
14. Price, WN. Big data and black-box medical algorithms. Sci Transl Med. 2018;10(471):pi:eaao5333.
15. Antman EM, Loscalzo J. Precision medicine in cardiology. Nat Rev Cardiol. 2016;13(10):591-602.
16. Price, WN II. Black Box medicine. Harvard J Law Tech. 2015;28(2):419-467.
17. Dey D, Slomka PJ, Leeson P, Comaniciu D, Shrestha S, Sengupta PP, et al. Artificial intelligence in cardiovascular imaging: JACC State-of-the-Art review. J Am Coll Cardiol. 2019;73(11):1317-35.
18. Shameer K, Johnson KW, Glicksberg BS, Dudley JT, Sengupta PP. Machine learning in cardiovascular medicine: are we there yet? Heart. 2018;104(14):1156-64.
19. Al'Aref SJ, Anchouche K, Singh G, Slomka PJ, Kolli KK, Kumar A, et al. Clinical applications of machine learning in cardiovascular disease and its relevance to cardiac imaging. Eur Heart J. 2018;40(24):1975-86.
20. Somashekhar SP, Sepulveda MJ, Puglielli S, Norden AD, Shortliffe EH, Rohit Kumar C, et al. Watson for Oncology and breast cancer treatment recommendations: agreement with an expert multidisciplinary tumor board. Ann Oncol. 2018;29(2):418-23.
21. IBM. Watson. New York: IBM; 2019 [Cited in 2018 Oct 10]. Available from: https://www.ibm.com/watson/index.html.
22. Samad MD, Wehner GJ, Arbabshirani MR, Jing L, Powell AJ, Geva T, et al. Predicting deterioration of ventricular function in patients with repaired tetralogy of Fallot using machine learning. Eur Heart J Cardiovasc Imaging. 2018;19(7):730-8.
23. Berikol GB, Yildiz O, Özcan IT. Diagnosis of acute coronary syndrome with a support vector machine. J Med Syst. 2016;40(4):84.
24. Betancur J, Rubeaux M, Fuchs TA, Otaki Y, Arnson Y, Slipczuk L, et al. Automatic valve plane localization in myocardial perfusion SPECT/CT by machine learning: Anatomic and clinical validation. J Nucl Med. 2016;58(6):961-7.
25. Paredes S, Rocha T, de Carvalho P, Henriques J, Morais J, Ferreira J. Integration of different risk assessment tools to improve stratification of patients with coronary artery disease. Med Biol Eng Comput. 2015;53(10):1069-83.
26. Al-Mallah MH, Elshawi R, Ahmed AM, Qureshi WT, Brawner CA, Blaha MJ, et al. Using machine learning to the association between cardiorespiratory fitness and all-cause mortality (from the Henry Ford Exercise Testing Project). Am J Cardiol. 2017;120(11):2078-84.
27. Smisek R, Hejc J, Ronzhina M, Nemcova A, Marsanova L, Kolarova J, et al. Multi-stage SVM approach for cardiac arrhythmias detection in short single-lead ECG recorded by a wearable device. Physiol Meas. 2018;39(9):094003.
28. Stuckey TD, Gammon RS, Goswami R, Depta JP, Steuter JA, Meine FJ 3rd, et al. Cardiac phase space tomography: a novel method of assessing coronary artery disease utilizing machine learning. PLoS One. 2018;13(8):e0198603.
29. Samad MD, Ulloa A, Wehner GJ, Jing L, Hartzel D, Good CW, et al. Predicting survival from large echocardiography and electronic health record datasets: optimization with machine learning. JACC Cardiovasc Imaging. 2019;12(4):681-9.
30. Ambale-Venkatesh B, Yang X, Wu CO, Liu K, Hundley WG, McClelland R, et al. Cardiovascular event prediction by machine learning: the multi-ethnic study of atherosclerosis. Circ Res.2017;121(9):1092-101.
31. Ishwaran H, Kogalur UB, Blackstone EH, Lauer MS. Random survival forests. Ann Appl Stat. 2008;2(3):841-60.
32. Cikes M, Sanchez-Martinez S, Claggett B, Duchateau N, Piella G, Butakoff C, et al. Machine learning-based phenogrouping in heart failure to identify responders to cardiac resynchronization therapy. Eur J Heart Fail. 2019;21(1):74-85.
33. Kwon JM, Lee Y, Lee Y, Lee S, Park J. An algorithm based on deep learning for predicting in-hospital cardiac arrest. Am Heart Assoc. 2018;7(13):pii: e008678.
34. Rubin J, Parvaneh S, Rahman A, Conroy B, Babaeizadeh S. Densely connected convolutional networks for detection of atrial fibrillation from short single-lead ECG recordings. J Electrocardiol. 2018;51(6S):S18-S21.
35. Zhang J, Gajjala S, Agrawal P, Tison GH, Hallock LA, Beussink-Nelson L, et al. Fully automated echocardiogram interpretation in clinical practice. Circulation. 2018;138(16):1623-35.
36. Nakajima K, Kudo T, Nakata T, Kiso K, Kasai T, Taniguchi Y, et al. Diagnostic accuracy of an artificial neural network compared with statistical quantitation of myocardial perfusion images: a Japanese multicenter study. Eur J Nucl Med Mol Imaging. 2017;44(13):2280-9.
37. Mortazavi BJ, Bucholz EM, Desai NR, Huang C, Curtis JP, Masoudi FA, et al. Comparison of machine learning methods with national cardiovascular data registry models for prediction of risk of bleeding after percutaneous coronary intervention. JAMA Netw Open. 2019;2(7):e196835.
38. Hernesniemi JA, Mahdiani S, Tynkkynen JA, Lyytikäinen LP, Mishra PP, Lehtimäki T, et al. Extensive phenotype data and machine learning in prediction of mortality in acute coronary syndrome - the MADDEC study. Ann Med. 2019;51(2):156-63.
39. Nannen V. The Paradox of Overfitting Volker Nannen. [thesis] . Países Baixos: Faculty of Artificial Intelligence at the University of Groningen; 2003.
40. Cortes C, Vapnik V. Support-vector networks. Mach Learn. 1995;20:273-97.

41. Bayes T. An essay towards solving a problem in the doctrine of chances. By the late Rev. Mr. Bayes, F. R. S. communicated by Mr. Price, in a letter to John Canton, A. M. F. R. S. Philos Trans R Soc Lond. 1763;53: 370-418.

42. Webb GI, Boughton JR, Wang Z. Not so naive bayes: aggregating one-dependence estimators. Mach Learn. 2005;58(1):5-24.

43. Watkins, DS. Fundamentals of matrix computations. 2th ed. New York: Wiley-Interscience; 2002.

44. Cover T, Hart P. (1967). Nearest neighbor pattern classification. IEEE Trans Inf Theory. 1967;13(1):21-7.

45. Fix, E., Hodges, J.L. Discriminatory analysis, nonparametric discrimination: Consistency properties. Technical Report 4, USAF School of Aviation Medicine, Randolph Field, Texas, 1951.

46. Holland JH. Adaptation in natural and artificial systems. 2th ed. Cambridge, MA: MIT Press; 1992.

47. Breiman L. Random forests. Mach Learn. 2001;45(1):5-32.

48. Ho TK. Random decision forests. In: Proceedings of the 3rd International Conference on Document Analysis and Recognition; 1995 Aug 14-16; Montreal. Washington, DC: IEEE Computer Society; 1995. p.278-82.

49. MacQueen JB. Some Methods for classification and Analysis of Multivariate Observations. Proc. Fifth Berkeley Symp. on Math. Statist. and Prob. 1967;1:281-97.

50. McCulloch WS, Pitts W. A logical calculus of ideas immanent in nervous activity. Bull Math Biophys. 1943;5(4):115-33.

51. Rosenblatt F. The perceptron: a probabilistic model for information storage and organization in the brain. Psychol Rev. 1958;65(6):386-408.

52. Broomhead DS, Lowe D. Multivariable functional interpolation and adaptive networks. Complex Syst. 1988;2:321-55.

53. Friedman JH. Greedy function approximation: a gradient boosting machine. Ann Stat. 2001;29(5):1189-232.

54. Friedman JH. Stochastic gradient boosting. Comput. Stat. Data Anal. 2002;38(4):367-78.

55. Wang Y, Kosinski M. Deep neural networks are more accurate than humans at detecting sexual orientation from facial images. J Pers Soc Psychol. 2018;114(2):246-57.

56. Ma H, Marti-Gutierrez N, Park SW, Wu J, Lee Y, Suzuki K, et al. Correction of a pathogenic gene mutation in human embryos. Nature. 2017;548(7668):413-9.

57. Shah SJ, Katz DH, Deo RC. Phenotypic spectrum of heart failure with preserved ejection fraction. Heart Fail Clin. 2014;10(3):407-18.

58. Medina EL, Mesquita CT, Loques Filho O. Healthcare social networks for patients with cardiovascular diseases and recommendation systems. Int J Cardiovasc Sci. 2016;29(1):80-5.

59. Bittencourt MS. From evidence-based medicine to precision health: using data to personalize care. Arq Bras Cardiol. 2018;111(6):762-3.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Internet Search Trends and Regional Mortality Tendencies: The Case of Oral Anticoagulants and Stroke

Roberto Muniz Ferreira,[1,2] *Ísis da Capela Pinheiro,*[1,2] *João Roquette Fleury da Rocha*[1,2]

Universidade Federal do Rio de Janeiro – Instituto do Coração Édson Saad,[1] *Rio de Janeiro, RJ – Brazil*

Hospital Samaritano Botafogo – Cardiologia,[2] *Rio de Janeiro, RJ – Brazil*

Introduction

Multiple studies have found that up to 30% of ischemic strokes are associated with atrial fibrillation (AF), especially in the elderly population.[1,2] Although the embolic risk varies according to clinical characteristics and comorbidities, anticoagulant therapy has consistently shown to reduce stroke rates by approximately 70%.[1] However, previous studies demonstrated that treatment rates with warfarin were low, even in patients at high risk for embolic events. Despite evidence from various publications demonstrating the effectiveness and safety of vitamin K antagonists, their complex pharmacokinetics and the need for continuous monitoring and frequent dose adjustments were the main explanations for low adherence.[3]

Over the last 10 years, four direct oral anticoagulants (DOAC) have become available to prevent embolic events in patients with non-valvular AF: dabigatran, rivaroxaban, apixaban and edoxaban. In August 2011, dabigatran was the first DOAC approved in Brazil for stroke prevention, followed by rivaroxaban four months later. Two years later, apixaban was also introduced in the Brazilian market and only in February 2018 edoxaban became available. When compared to warfarin, multiple trials have suggested that DOACs are non-inferior in preventing ischemic strokes and possibly superior in reducing mortality, perhaps due to fewer intracranial hemorrhages.[4] In addition to waive the need for laboratory monitoring, they have more predictable pharmacokinetics and a lower incidence of drug-to-drug interactions. Recent studies have demonstrated an increase in anticoagulation prescription rates among physicians since DOACs have become clinically available.[1]

The analysis of Internet search trends is a promising method for estimating the frequency by which medical interventions are being applied in clinical practice. More recent publications have suggested a strong correlation between Internet search engine query data, medical decision making and pharmacological prescription patterns for a given region.[5] However, it is not clear whether these search patterns are also predictive of regional trends associated with clinical events.

Keywords

Stroke/prevention and control; Myocardial Ischemia/prevention and control; Pharmaceutical Services, Online/trends; Anticoagulants/therapeutic use; Varfarin; Dabigatran; Rivaroxaban; Mortality/trends.

Mailing Address: Roberto Muniz Ferreira •
Universidade Federal do Rio de Janeiro - Instituto do Coração Édson Saad - Rua Rodolpho Paulo Rocco, 255. Postal Code 21941-913, Rio de Janeiro, RJ – Brazil
E-mail: betomf@terra.com.br
Manuscript received November 02, 2019, revised manuscript December 02, 2019, accepted December 27, 2019

Internet search trends in health care

Currently, Google is perhaps the most utilized online search tool, even among healthcare professionals. The search patterns created within Google have been available since 2004 and can be accessed from Google Trends (Google Inc. Mountain View, CA, USA). Briefly, this is an open-access tool which displays how frequently any given term or topic has been searched for in the Google search engine. Additionally, filters can be used to specify a region and time period for the analysis. The frequency is presented as a number from 0 to 100 which varies over the predefined time interval and represents a proportion in relation to the highest popularity point. Accordingly, a value of 100 indicates the moment at which the term or topic reached the highest search interest, and a value of zero correlates to less than 1% of the peak popularity.[6] Also, up to five terms or topics can be analyzed simultaneously, and a mean popularity value is automatically provided for each term during the selected interval.

Internet search engines have the potential to reflect the general interest of a population in a given topic, within a specific time interval and region. Google Trends is an example of such a tool, and the scores provided the website are a result of many factors that directly influence the public's awareness regarding the subject being researched. These include promotional campaigns, media coverage, internet access, literacy rates and socioeconomic status. Nevertheless, when patients and health care professionals are exposed to information and knowledge, there is a higher probability of an informed decision regarding the implementation of medical interventions.

A study by Kritz et al.[7] demonstrated that physicians frequently use general search engines to retrieve medical knowledge in daily practice, chiefly because of lack of time for a more thorough research.[7] Furthermore, some countries use search engines as epidemiological surveillance tools for a variety of diseases, which could have implications in public health policies. In France, the Sentinel Network is a public health monitoring system where general practitioners use web-based data to follow disease patterns and potentially identify outbreaks at an early stage.[8]

Although popularity scores do not necessarily mirror drug prescription patterns, previous studies with a wide variety of medications have suggested that an association does in fact

DOI: https://doi.org/10.36660/abc.20190768

exist. This association has been shown with statins and several non-cardiovascular drugs.[9,10] A previous study by Lippi et al.[6] also found an increase in worldwide online search volume for DOACs, which has been consistent with the escalation in clinical use.

Internet search trends for oral anticoagulants and stroke

Despite a progressive increase in the number of publications in this area, an association between specific patterns of treatment search and subsequent variations in populational clinical events has yet to be clearly demonstrated. If a relationship really exists, search data would have the potential to function as a surrogate for large-scale effects of a given drug or intervention regarding specific clinical outcomes. The influence of oral anticoagulants in the epidemiology of stroke-related deaths serves as an adequate example in this scenario, considering that most ischemic cerebrovascular events are cardioembolic and effectively prevented by oral anticoagulants. Hernandez et al.[11] have previously correlated geographic variation in the use of anticoagulation with stroke rates among Medicare beneficiaries, demonstrating an inverse relationship between the two variables.[11]

According to the Department of Information Technology of the Brazilian Unified Health System (DATASUS), the total number of stroke-related deaths in Brazil declined between 2006 and 2015, although the most significant reduction was after 2011.[12] In addition, ischemic strokes and those not classified as a specific type (ICD-10 codes I63 and I64) comprised most of the cerebrovascular events (70,2%), and presented a similar pattern of decline since 2011 (mean of 49,406.4 ± 451 vs. 46,447.2 ± 1633 deaths per year before and after 2011, respectively). Conversely, hemorrhagic stroke deaths (ICD-10 codes I60, I61 and I62) increased in the same period, albeit at a much lower proportion (mean of 19,740.4 ± 278 vs 20,933.8 ± 446 deaths per year before and after 2011, respectively).[13]

During the same period, when warfarin, dabigatran and rivaroxaban were used as search topics ("drug") and Brazil was defined as the only search region, there was a clear tendency for a decline in warfarin's Google Trends search scores after 2011. In 2015 the popularity value reached approximately the same level as 2009. Conversely, rivaroxaban's score increased considerably after 2011, and surpassed warfarin's popularity after 2013. Dabigatran's search score remained consistently below the other two anticoagulants throughout the analyzed time interval. It should be noted that when a topic (i.e. "drug") is used as the search option, terms that are associated with the corresponding drug, including commercial names, are also contemplated.

When stroke-related deaths and search scores are appreciated in combination there appears to be an inverse correlation with ischemic strokes and a positive association with hemorrhagic events. Between 2011 and 2015, total and ischemic stroke deaths decreased (Figure 1) and hemorrhagic events increased (Figure 2) concurrently to an escalation in DOAC Google Trends' search scores. Most importantly, this relationship seemed to be primarily driven by a rise in rivaroxaban's popularity.

Since there has been a progressive increase in the prescription of oral anticoagulants in clinical practice, and also a rise in the internet popularity of DOAC worldwide, changes in the incidence of both ischemic and hemorrhagic cerebrovascular events may be anticipated.[1,6] In Brazil, such an impact would also be expected, since in 2015 rivaroxaban was already the drug with the third highest sales revenue in the national market, only four years after it became available to the public.[14] In only two years, rivaroxaban surpassed warfarin in Internet search volume in most of the country. This finding is probably related to an increase in the use of DOACs, rather than a transition between anticoagulant categories. DOACs have become attractive options when stroke prevention is considered in AF, mainly because of their predictable pharmacokinetics, probably safer profile and non-inferior effectiveness when compared to vitamin K antagonists.

Contrary to what was found with ischemic strokes, hemorrhagic stroke-related deaths apparently increased since 2011. Although such an escalation occurred at a lower rate, the trend also appeared to be related to rivaroxaban´s search patterns. Perhaps this tendency was also a result of a greater number of previously untreated patients that progressively received anticoagulants, since DOACs tend to reduce intracranial bleeding when compared to warfarin.

The greater adoption of the CHA_2DS_2-Vasc Score could also have contributed in expanding the number of patients on anticoagulant therapy during the study period.[1] Furthermore, considering that total stroke deaths decreased significantly, the epidemiological pattern is comparable to the net benefit of DOACs that has been found in multiple trials.[4] The possibility that other factors, such as public health policies, greater cardiovascular risk factor control and improvements in socioeconomic conditions, may have influenced the annual number of deaths cannot be entirely excluded. However, a reduction in hemorrhagic stroke-related deaths would be expected solely from these interventions. Until 2017, a persistent decline in ischemic deaths was still observed, whereas hemorrhagic events continued to increase.[12]

Although search scores may provide an estimate of prescription patterns, they are not a direct reflection of regional drug utilization or sales. Internet access in 2014 was available in approximately 50% of all households in Brazil and the illiteracy rate in individuals over 65 years of age was still high (26.4%).[15] As such, these patterns must be interpreted considering all of the potential biases, especially because the specific algorithms that were employed by Google Trends were not disclosed. Nevertheless, as Internet access expands throughout the World and new policies are developed to reduce illiteracy rates, search trends will become increasingly more correlated to daily behavioral patterns.

Conclusion

The progressive worldwide populational growth has demanded the development of new mechanisms to monitor epidemiological changes in both treatment tendencies and disease patterns. In this context, the Internet has become a valuable tool for gathering information to aid in daily decision making, particularly in health care, where the critical

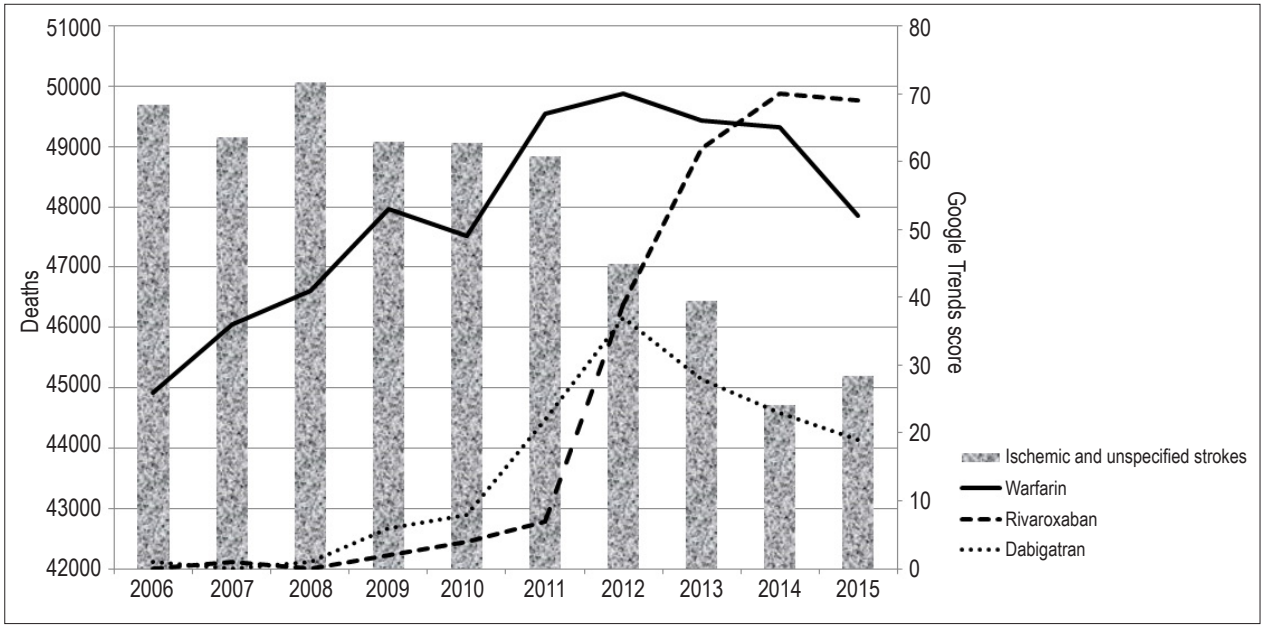


Figure 1 – *Annual ischemic stroke-related deaths and mean Google Trends scores for anticoagulants. After 2011, an increase in the online popularity of rivaroxaban was accompanied by a decrease in the number of ischemic stroke related-deaths in Brazil.*

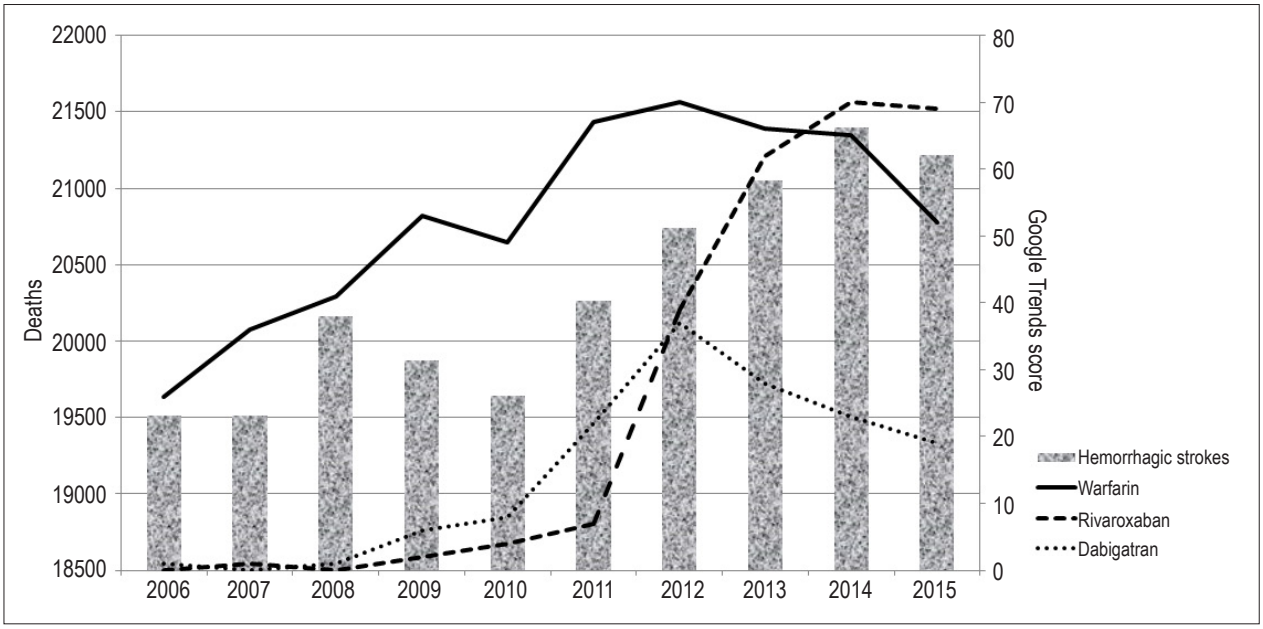


Figure 2 – *Annual hemorrhagic stroke-related deaths and mean anticoagulant Google Trends scores. After 2011, an increase in rivaroxaban's online popularity was accompanied by an escalation in the total number of hemorrhagic stroke related-deaths in Brazil.*

appraisal of the collected data is also of upmost importance. Over the last 10 years, the increasing clinical experience with DOACs in patients with AF has been accompanied by a significant global rise in the popularity of these drugs in Internet search engines. This phenomenon also appears to be occurring in middle-income countries, such as Brazil. However, the association between web-based tendencies and clinical outcomes is still an area that needs further investigation. There is a possibility that the effectiveness of large-scale health care policies and interventions, such as vaccination campaigns, may be monitored by online search data, especially in regions where most of the population

have access to the internet. Specific areas in medicine where this strategy may be of value are yet to be determined and should be explored in future studies.

Acknowledgements

This study was supported by the Federal University of Rio de Janeiro and the Edson Saad Heart Institute.

Author contributions

Conception and design of the research, analysis and interpretation of the data, writing of the manuscript and critical revision of the manuscript for intellectual content: Ferreira RM, Pinheiro IC, Rocha JRF; Acquisition of data and Statistical analysis: Ferreira RM.

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. Katz D, Maddox T, Turakhia M, Gehi A, O'Brien E, Lubitz S, et al. Contemporary Trends in Oral Anticoagulant Prescription in Atrial Fibrillation Patients at Low to Moderate Risk of Stroke After Guideline-Recommended Change in Use of the CHADS 2 to the CHA 2 DS 2 -VASc Score for Thromboembolic Risk Assessment. Circ Cardiovasc Qual Outcomes. 2017;10(5):e003476.
2. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Eur Heart J. 2016;37(38):2893-962.
3. Buckingham T, Hatala R. Anticoagulants for atrial fibrillation: Why is the treatment rate so low?. Clin Cardiol. 2002;25(10):447-54.
4. López-López J, Sterne J, Thom H, Higgins J, Hingorani A, Okoli J, et al. Oral anticoagulants for prevention of stroke in atrial fibrillation: systematic review, network meta-analysis, and cost effectiveness analysis. BMJ. 2017;359:j5631.
5. Moat H, Olivola C, Chater N, Preis T. Searching Choices: Quantifying Decision-Making Processes Using Search Engine Data. Top Cogn Sci. 2016;8(3):685-96.
6. Lippi G, Mattiuzzi C, Cervellin G, Favaloro E. Direct oral anticoagulants: analysis of worldwide use and popularity using Google Trends. Ann Transl Med. 2017;5(16):322.
7. Kritz M, Gschwandtner M, Stefanov V, Hanbury A, Samwald M. Utilization and Perceived Problems of Online Medical Resources and Search Tools Among Different Groups of European Physicians. J Med Internet Res. 2013;15(6):e122.
8. Blanchon T. Web-based sentinel provider surveillance network in France. In: Nkuchia M, Lynfield R, Van Beneden CA, de Valk H, eds. Infectious dsease surveillance. Philadelphia: Willey-Blackwell; 2013. p.418-25.
9. Simmering J, Polgreen L, Polgreen P. Web search query volume as a measure of pharmaceutical utilization and changes in prescribing patterns. Res Social Adm Pharm 2014;10(6):896-903.
10. Schuster N, Rogers M, McMahon L. Using Search Engine Query Data to Track Pharmaceutical Utilization: A Study of Statins. Am J Manag Care 2010;16(8): e215–9.
11. Hernandez, I., Saba, S. and Zhang, Y. Geographic Variation in the Use of Oral Anticoagulation Therapy in Stroke Prevention in Atrial Fibrillation. Stroke 2017;48(8):2289-91.
12. Brasil. Ministério da Saúde. Datasus. Informações estatísticas da saúde. Brasilia; 2018.
13. World Health Organization . (WHO). International Classification of Diseases. Washington; 2018.
14. Interfarma. Associação da Indústria Farmacêutica de Pesquisa; Guia 2016 Interfarma. São Paulo; 2016.
15. Instituto Brasileiro de Geografia e Estatística. (IBGE). Indicadores 2015. Rio de Janeiro; 2018.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Evolved Inferior Wall Myocardial Infarction with Left Ventricular Pseudoaneurysm: A Diagnostic Dilemma

Sónia Gomes Coelho,[1] Clara F. Jorge,[1] Pedro B. Carlos,[1] Anne Delgado,[2] Leopoldina Vicente[1]

Centro Hospitalar Cova da Beira EPE - Department of Internal Medicine,[1] Covilhã - Portugal

Centro Hospitalar Cova da Beira EPE - Department of Cardiology,[2] Covilhã - Portugal

Introduction

The left ventricular (LV) pseudoaneurysm (PA) is a rare mechanical complication of acute myocardial infarction (AMI).[1] It results from myocardial rupture, in which the hemorrhagic process is contained by the adherent pericardium. It occurs most commonly in the inferior and posterior ventricular wall, since the rupture of the anterior ventricular wall usually leads to cardiac tamponade and immediate death, while the inferior-posterior face of the heart rests on the diaphragm, facilitating the ventricular cavity containment by the pericardium.[1-3] Imaging methods are crucial to establish the diagnosis. Transthoracic (TTE) and transesophageal echocardiography (TEE) allow the definitive diagnosis in 26% and 75% of cases, respectively.[1,2] Cardiac magnetic resonance (CMR) imaging is useful in the differential diagnosis of LV PA and aneurysm, with a reported sensitivity of 100%.[2] The presence of late pericardial enhancement in the CMR is highly suggestive of LV PA, which may represent the effect of the passage of blood into the pericardial space at the time of myocardial rupture, with subsequent pericardial inflammation and fibrosis.[1,2,4]

Case Report

An 87-year-old female patient, with a relevant personal history of dyslipidemia, multinodular goiter and right renal cyst, came to the Emergency Department (ED) due to clinical symptoms, with 3 weeks of evolution, characterized by frequent tiredness and dyspnea at small efforts, mild and persistent precordial pain with dorsal irradiation, anorexia and nausea. She was hemodynamically stable, had bilateral rales, and no other significant alterations on physical examination. The electrocardiogram showed ST-segment elevation at the DII, DIII and aVF leads. Laboratory tests showed increased troponin I (551.1 ng/L) and NT-proBNP (12,568 pg/mL) levels. The patient was admitted with the diagnosis of AMI with lower ST-segment elevation (STEMI). Taking into account the time of evolution, the case was considered as having no indication for fibrinolysis. The TTE showed biventricular dysfunction (LV ejection fraction of 40% by the Simpson Biplane method), posterolateral and lower mid-basal akinesia with aneurysmal formation (Figure 1), moderate mitral regurgitation and moderate pulmonary arterial hypertension. She was submitted to an ischemia test (myocardial perfusion scintigraphy) with no evidence of ischemia, but a fixed defect was documented in the lower wall, thus not being a candidate for coronary angiography. The patient was discharged under clinical stability and treated with dual antiplatelet therapy, statin and beta-blocker (low dose). Two days later, she returned to the ED with clinical signs suggestive of heart failure. The patient had tachycardia, polypneia, and required supplemental oxygen therapy. Radiologically, bilateral pleural effusion was visualized. The ECG showed no dynamic alterations. The TTE was repeated, showing moderate pericardial effusion, with no signs of hemodynamic compromise, and an increase in the aneurysm size, raising the possibility of its being a PA (Figure 2). She underwent CMR in another institution (Figures 3 and 4), which confirmed that it was 7x5.4 cm lower ventricular wall PA, with a wide neck (3.5 cm), and a parietal thrombus. The case was discussed with the Cardiothoracic Surgery team, which, taking into account the patient's advanced age, state of fragility and clinical picture irreversibility, considered that the patient had high intra- and perioperative morbidity and mortality, and thus would not benefit from surgical treatment. The patient developed cardiogenic shock and died after four days of hospitalization.

Keywords

Myocardial Infarction/complications; Pseudoaneurysm; Heart Rupture; Echocardiography/methods; Magnetic Resonance Spectroscopy/methods.

Mailing Address: Sónia Gomes Coelho •
Centro Hospitalar Cova da Beira EPE - Quinta do Alvito, 6200-251, Covilhã - Portugal
E-mail: s.coelho88@gmail.com
Manuscript received November 19, 2019, revised manuscript January 12, 2020, accepted February 19, 2020

DOI: https://doi.org/10.36660/abc.20200029

Author contributions

Acquisition of data: Coelho SG, Jorge CF, Carlos PB, Delgado A, Vicente L; Analysis and interpretation of the data: Coelho SG, Jorge CF, Carlos PB, Delgado A, Vicente L; Writing of the manuscript: Coelho SG; Critical revision of the manuscript for intellectual content: Coelho SG, Jorge CF, Carlos PB, Delgado A, Vicente L.

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.

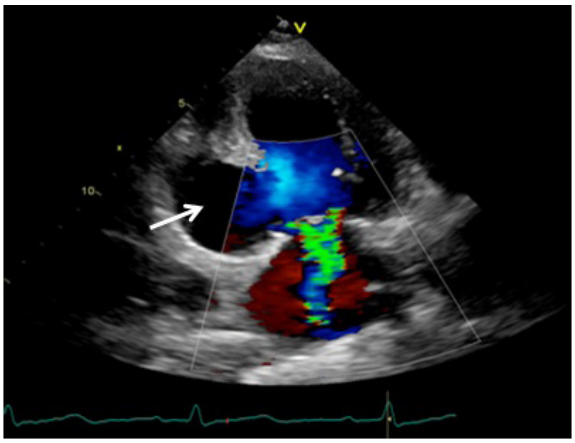


Figure 1 - *Transthoracic echocardiography (apical 2-chamber view) showing aneurysmal formation (arrow).*

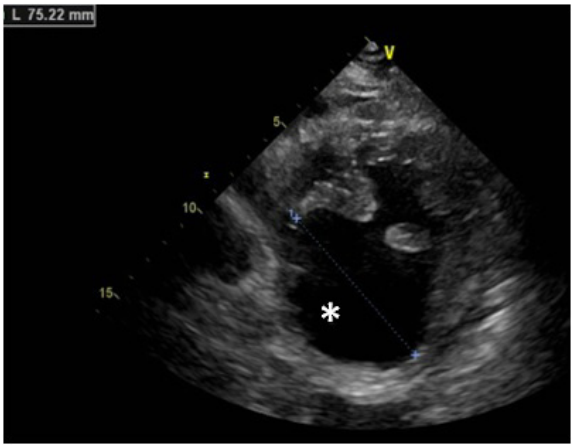


Figure 2 - *Transthoracic echocardiography (short axis view) suggestive of a pseudoaneurysm of the lower left ventricular wall (asterisk).*

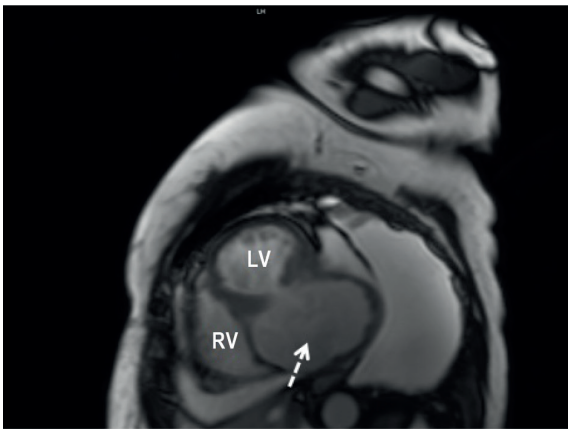


Figure 3 - *Cardiac magnetic resonance imaging (static cine image, short axis) confirming the presence of a large left ventricular pseudoaneurysm (dashed arrow). RV, right ventricle; LV, left ventricle.*

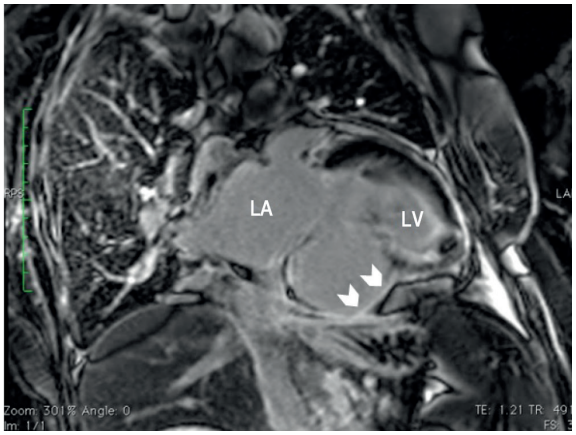


Figure 4 - *Cardiac magnetic resonance imaging, after gadolinium injection, showing the presence of late enhancement over the pericardial leaflets (arrowheads), supporting the diagnosis of pseudoaneurysm. LA, left atrium; LV, left ventricle.*

References

1. Faustino M, Ranchordás S, Abecasis J, Freitas A, Ferreira M, Gil V, et al. Pseudoaneurisma ventricular esquerdo – um desafio diagnóstico. Rev Port Cardiol. 2016; 35(6):373.e1-373.e6.
2. Inayat F, Ghani AR, Riaz I, Ali NS, Sarwar U, Bonita R, et al. Left Ventricular Pseudoaneurysm: An Overview of Diagnosis and Management. J Investig Med High Impact Case Rep. 2018 Aug 2;6:2324709618792025
3. Falcão JLAA, Falcão SNRS, Garcia MFMA, Arruda ALMA, Hueb AC, Jatene FB, et al. Pseudoaneurisma de Ventrículo Esquerdo Associado a Insuficiência Mitral Grave Complicando Infarto Agudo do Miocárdio Ínfero-Látero-Dorsal. Arq Bras Cardiol. 2005;84(6):488-91.
4. Oliveira SM, Dias P, Pinho T, Gavina C, Almeida PB, Madureira AJ, et al. Pseudoaneurisma gigante do ventrículo esquerdo: contributo diagnóstico de diferentes modalidades de imagem não invasivas. Rev Port Cardiol. 2012; 31(6):439-44.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Inotropic and Antiarrhythmic Transmural Actions of Ranolazine in a Cellular Model of Type 3 Long QT Syndrome

Victor Martins Miranda,[1] *Samuel Santos Beserra,*[1] *Danilo Roman-Campos*[1]

Universidade Federal de São Paulo, Departamento de Biofísica, Edifício de Ciências Biomédicas,[1] *São Paulo, SP - Brazil*

Abstract

Ranolazine (RANO) prevents cardiac arrhythmia by blocking the late sodium current (I_{NaL}). A transmural gradient of Nav1.5 is found in the left ventricular wall of the heart. Thus, we investigated the effects of RANO in healthy cardiomyocytes and in a cellular model of type 3 long QT syndrome (LQT3). We used isolated endocardium (ENDO) and epicardium (EPI) cells and a video edge detection system and fluorescence microscopy to monitor calcium transients. RANO (0.1, 1, 10 and 30 uM, at 25°C) at a range of pacing frequencies showed a minor impact on both cell types, but RANO at 30uM and 35°C for ENDO cells attenuated sarcomere shortening by~21%. Next, to mimic LQT3, we exposed ENDO and EPI cells to anemone toxin II (ATX-II), which augments I_{NaL}. Cellular arrhythmias induced by ATX-II were abrogated by RANO (30 μM) at 35°C. Based on our results we can conclude that RANO has a minor impact on sarcomere shortening of healthy ENDO and EPI cells and it abrogates arrhythmias induced by I_{NaL} to a similar level in ENDO and EPI cells.

Introduction

Arrhythmia in cardiovascular diseases is one of the leading causes of death worldwide.[1] The antiarrhythmic action of RANO is attributed to reduction in the slow inactivating component of cardiac inward current through Nav1.5, known as the late sodium current (I_{NaL}).[2] Despite major advances in the understanding of molecular mechanisms underlying RANO action, whether RANO exhibits a transmural action in heart muscle cells remains uncertain. Therefore, in the present study our hypothesis is that RANO has transmural action on healthy field-stimulated endocardium (ENDO) and epicardium (EPI) cells and also on arrhythmias and calcium disturbance induced by anemone toxin II (ATX-II),[3] which increases I_{NaL} and mimics several aspects of type 3 long QT syndrome (LQT3), a diseased linked to increased I_{NaL} in heart cells.[2]

Keywords

Arrhythmias, Type 3 Long QT Syndrome, ATX-II, Late Sodium current, Ranolazine, Contraction.

Mailing Address: Danilo Roman Campos •
Universidade Federal de São Paulo – Biofísica - Rua Botucatu, 862.
Postal Code 04023-062, São Paulo, SP – Brazil
E-mail: drcbio@gmail.com
Manuscript received April 03, 2019, revised manuscript August 19, 2019, accepted September 10, 2019

Methods

Animals

Male Wistar rats (160–250 g; 5–7-week old) were used in the experiments. All experimental procedures were performed in accordance with institutional guidelines, and the study was approved by the local ethical review committee. Cardiomyocytes were isolated as previously described.[4]

Sarcomere shortening and calcium transient

Experiments were conducted as previously described by our group.[5] Cells were perfused with RANO (Alomone, Israel) at 0.1, 1, 10, or 30 μM from a 10 mM stock solution. Data were normalized as the function of sarcomere contraction before RANO exposure. To access the antiarrhythmic effect of RANO following exposure to 6 nM ATX-II (Alomone, Israel), the times to 90% sarcomere relaxation (T90R) and calcium reuptake (T90Ca^{2+}) were recorded as arrhythmic indexes. In addition, 10 mM tetrodotoxin (TTX) (Alomone, Israel) was used to confirm that the observed phenotype was indeed due to I_{NaL}.

Statistical analysis

All results are expressed as mean ± standard error of the mean. Significant differences were determined using two-sample t-test or one-way ANOVA with repeated measures, followed by Tukey's post hoc test. $P < 0.05$ was considered significant. Cardiomyocytes from at least two distinct hearts were used in each experiment.

Results and discussion

Previous studies have shown that healthy cardiomyocytes exhibit I_{NaL}.[6] Moreover, a gradient of sodium current has been recorded in the left ventricular wall, and it has been reported to be larger in ENDO cells than in EPI cells.[7] Thus, we hypothesized that ENDO cells present larger I_{NaL} than EPI cells. Since I_{NaL} modulates $[Ca^{2+}]i$ in cardiomyocytes,[8] RANO would be able to attenuate contraction in both cell groups, although with greater potency in ENDO cells than in EPI cells. To test this hypothesis, cells were perfused at 25°C with RANO; however, RANO could not attenuate sarcomere shortening in ENDO and EPI cardiomyocytes (Figures 1 A and C). A similar trend was observed when cardiomyocytes were exposed to 30 μM RANO and paced at 0.2 Hz. When ENDO and EPI cells were exposed to 30 μM RANO and paced at 0.2 Hz using a superfusion solution at 35°C, cell shortening was attenuated in ENDO cells by ~21% ($p < 0.05$) but not in EPI cells (Figures 1B and D). Thus, corroborating the previous findings, our results suggest that healthy ENDO cells indeed

DOI: https://doi.org/10.36660/abc.20190220

Inotropic and Antiarrhythmic Transmural Actions of Ranolazine in a Cellular Model of Type 3 Long QT Syndrome

Victor Martins Miranda,[1] *Samuel Santos Beserra,*[1] *Danilo Roman-Campos*[1]

Universidade Federal de São Paulo, Departamento de Biofísica, Edifício de Ciências Biomédicas,[1] *São Paulo, SP - Brazil*

Abstract

Ranolazine (RANO) prevents cardiac arrhythmia by blocking the late sodium current (I_{NaL}). A transmural gradient of Nav1.5 is found in the left ventricular wall of the heart. Thus, we investigated the effects of RANO in healthy cardiomyocytes and in a cellular model of type 3 long QT syndrome (LQT3). We used isolated endocardium (ENDO) and epicardium (EPI) cells and a video edge detection system and fluorescence microscopy to monitor calcium transients. RANO (0.1, 1, 10 and 30 uM, at 25°C) at a range of pacing frequencies showed a minor impact on both cell types, but RANO at 30uM and 35°C for ENDO cells attenuated sarcomere shortening by~21%. Next, to mimic LQT3, we exposed ENDO and EPI cells to anemone toxin II (ATX-II), which augments I_{NaL}. Cellular arrhythmias induced by ATX-II were abrogated by RANO (30 μM) at 35°C. Based on our results we can conclude that RANO has a minor impact on sarcomere shortening of healthy ENDO and EPI cells and it abrogates arrhythmias induced by I_{NaL} to a similar level in ENDO and EPI cells.

Introduction

Arrhythmia in cardiovascular diseases is one of the leading causes of death worldwide.[1] The antiarrhythmic action of RANO is attributed to reduction in the slow inactivating component of cardiac inward current through Nav1.5, known as the late sodium current (I_{NaL}).[2] Despite major advances in the understanding of molecular mechanisms underlying RANO action, whether RANO exhibits a transmural action in heart muscle cells remains uncertain. Therefore, in the present study our hypothesis is that RANO has transmural action on healthy field-stimulated endocardium (ENDO) and epicardium (EPI) cells and also on arrhythmias and calcium disturbance induced by anemone toxin II (ATX-II),[3] which increases I_{NaL} and mimics several aspects of type 3 long QT syndrome (LQT3), a diseased linked to increased I_{NaL} in heart cells.[2]

Keywords

Arrhythmias, Type 3 Long QT Syndrome, ATX-II, Late Sodium current, Ranolazine, Contraction.

Mailing Address: Danilo Roman Campos •
Universidade Federal de São Paulo – Biofísica - Rua Botucatu, 862.
Postal Code 04023-062, São Paulo, SP – Brazil
E-mail: drcbio@gmail.com
Manuscript received April 03, 2019, revised manuscript August 19, 2019, accepted September 10, 2019

Methods

Animals

Male Wistar rats (160–250 g; 5–7-week old) were used in the experiments. All experimental procedures were performed in accordance with institutional guidelines, and the study was approved by the local ethical review committee. Cardiomyocytes were isolated as previously described.[4]

Sarcomere shortening and calcium transient

Experiments were conducted as previously described by our group.[5] Cells were perfused with RANO (Alomone, Israel) at 0.1, 1, 10, or 30 μM from a 10 mM stock solution. Data were normalized as the function of sarcomere contraction before RANO exposure. To access the antiarrhythmic effect of RANO following exposure to 6 nM ATX-II (Alomone, Israel), the times to 90% sarcomere relaxation (T90R) and calcium reuptake (T90Ca^{2+}) were recorded as arrhythmic indexes. In addition, 10 mM tetrodotoxin (TTX) (Alomone, Israel) was used to confirm that the observed phenotype was indeed due to I_{NaL}.

Statistical analysis

All results are expressed as mean ± standard error of the mean. Significant differences were determined using two-sample t-test or one-way ANOVA with repeated measures, followed by Tukey's post hoc test. $P < 0.05$ was considered significant. Cardiomyocytes from at least two distinct hearts were used in each experiment.

Results and discussion

Previous studies have shown that healthy cardiomyocytes exhibit I_{NaL}.[6] Moreover, a gradient of sodium current has been recorded in the left ventricular wall, and it has been reported to be larger in ENDO cells than in EPI cells.[7] Thus, we hypothesized that ENDO cells present larger I_{NaL} than EPI cells. Since I_{NaL} modulates $[Ca^{2+}]i$ in cardiomyocytes,[8] RANO would be able to attenuate contraction in both cell groups, although with greater potency in ENDO cells than in EPI cells. To test this hypothesis, cells were perfused at 25°C with RANO; however, RANO could not attenuate sarcomere shortening in ENDO and EPI cardiomyocytes (Figures 1 A and C). A similar trend was observed when cardiomyocytes were exposed to 30 μM RANO and paced at 0.2 Hz. When ENDO and EPI cells were exposed to 30 μM RANO and paced at 0.2 Hz using a superfusion solution at 35°C, cell shortening was attenuated in ENDO cells by ~21% ($p < 0.05$) but not in EPI cells (Figures 1B and D). Thus, corroborating the previous findings, our results suggest that healthy ENDO cells indeed

DOI: https://doi.org/10.36660/abc.20190220

present larger I_{NaL} than EPI cells. However, it is also important to note that 30 μM RANO could also block L-type calcium current in cardiomyocytes.[9]

To better understand the mechanism underlying sarcomere shortening induced by RANO, subsequent experiments were performed at 35ºC. Cardiomyocytes were loaded with Fura 2-AM to monitor calcium oscillation during cell contraction, and cells were exposed to ATX-II to increase I_{NaL} and induce an LQT3 phenotype3 (Figure 2). ENDO (Figures 2A, B and C) and EPI (Figures 2D, E and F) cells exposed to ATX-II showed clear calcium disturbances and simultaneous mechanical arrhythmias. RANO (30 μM) strongly attenuated the arrhythmic phenotype induced by ATX-II in both cell groups to a similar extent. To confirm that the arrhythmic phenotype observed in our experiments was truly attributed to I_{NaL}, cells were exposed to 6 nM ATX-II [Figure 2A (iv) and Figure 2D (iv)], following exposure to 10 μM TTX and 6 nM ATX-II [Figure 2A (v) and Fig 2D (v)]. The results confirmed that the observed arrhythmic phenotype occurred due to I_{NaL} augmentation. Despite the fact that rat ENDO cells present larger sodium currents than EPI cells,[7,10] the arrhythmic phenotype induced by ATX-II and the extent of antiarrhythmic effects of RANO were similar in both cell groups.

Interestingly, the therapeutic concentration range of RANO is 1–10 μM.[11] The apparent discrepancy in RANO potency may be explained by the fact that ATX-II at doses of 1–10 nM induces larger I_{NaL} in cardiomyocytes than that observed in cardiovascular disease.[3,6]

Conclusion

RANO exerted a minor impact on sarcomere shortening of healthy cardiomyocytes and abrogated arrhythmias induced by I_{NaL} to a similar extent in ENDO and EPI cells.

Author contributions

Conception and design of the research and Writing of the manuscript: Campos DR; Acquisition of data: Miranda VM, Beserra SS; Analysis and interpretation of the data and Statistical analysis: Miranda VM, Campos DR.

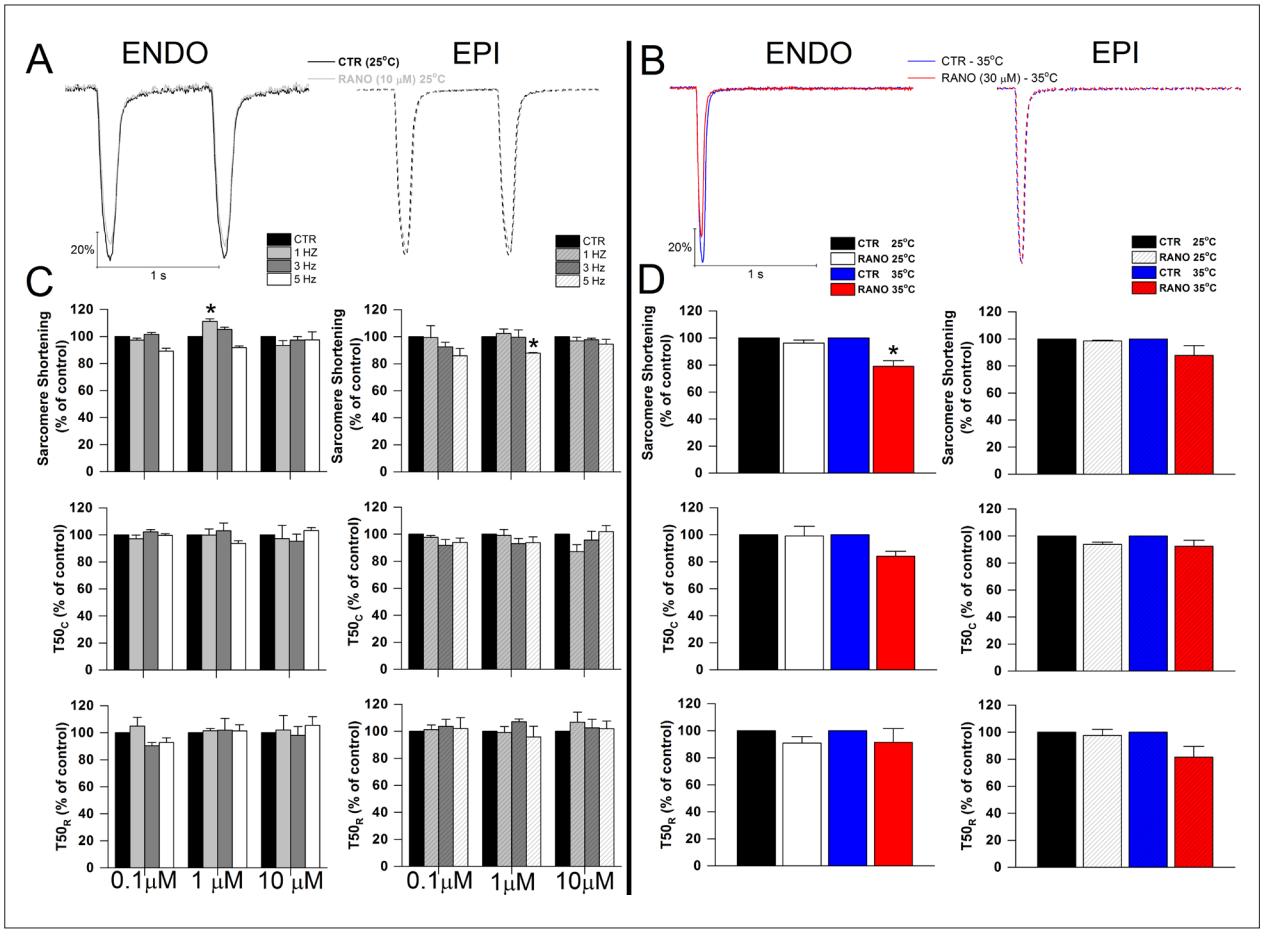


Figure 1 – *Inotropic effect of ranolazine (RANO) on sarcomere shortening of ENDO and EPI cardiomyocytes. Representative sarcomere shortening recordings before (black (25ºC) and blue (35ºC)) and after (light gray (25ºC) and red (35ºC)) exposure of ENDO (left) and EPI (right) cardiomyocyte to RANO ((A) 10 and (B) 30 μM). Inotropic effect of 0.1, 1, and 10 μM RANO (C) and 30 μM (D) on sarcomere shortening (upper bars); Normalized time to 50% sarcomere contraction (T50C) (middle bars)) and; normalized time to 50% of sarcomere relaxation (T50R) (bottom bars) Hatched bars represent EPI cells (n = 3–6 cells/concentration). *p < 0.05 comparing before and after RANO exposure.*

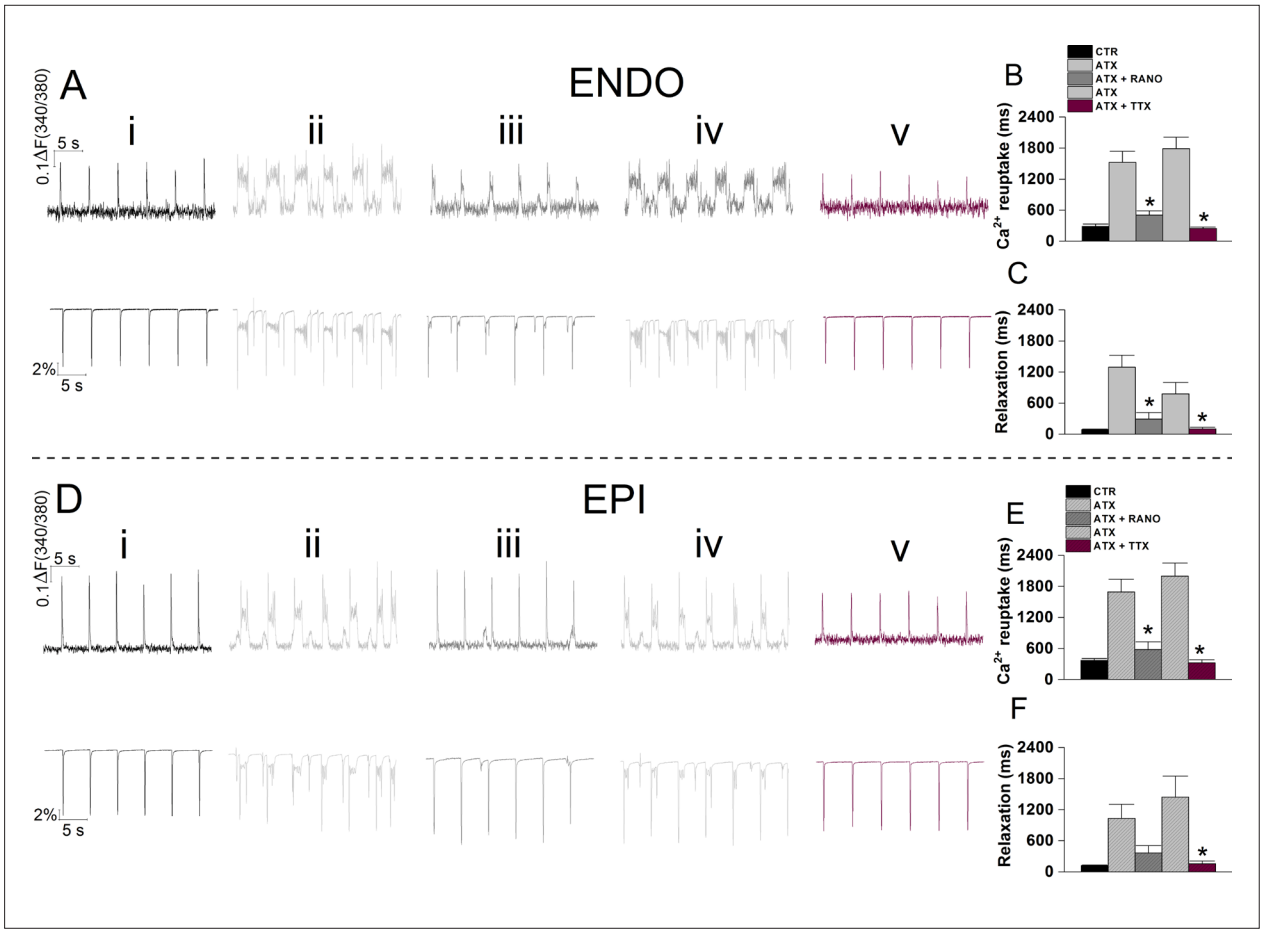


Figure 2 – *Action of ranolazine (RANO) in ENDO and EPI cardiomyocytes exposed to ATX-II and paced at 0.2 Hz. Representative traces of calcium transients (upper traces) and cardiomyocyte sarcomere shortening (lower traces) following exposure to Tyrode's solution (i), 6 nM ATX-II (ii), 6 nM ATX-II + 30 μM RANO (iii), 6 nM ATX-II (iv), and 6 nM ATX-II + 10 μM TTX (iv) in ENDO (A) and EPI (D) cells. Time to 90% of Ca2+ reuptake in ENDO (n = 8 cells) (B) and EPI (n = 6 cells) (E). Time to 90% sarcomere relaxation in ENDO (C) and EPI (F) cells. * p < 0.05 compared to the ATX-II group.*

Potential Conflict of Interest

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

Sources of Funding

This study was funded by FAPESP nº 2014/09861-1.

Study Association

This article is part of the thesis of master submitted by Victor Martins Miranda, from *Universidade Federal de São Paulo*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the CEUA UNIFESP under the protocol number 2435/70816. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

Erratum

In the Brief Communication "Inotropic and Antiarrhythmic Transmural Actions of Ranolazine in a Cellular Model of Type 3 Long QT Syndrome", with DOI number: https://doi.org/10.36660/abc.20190220, published in the periodical Arquivos Brasileiros de Cardiologia, 114(4):732-735, on page 732: consider Danilo Roman-Campos as the correct form for the name of the author Danilo Roman Campos.

References

1. Deo R, Albert CM. Epidemiology and genetics of sudden cardiac death. Circulation. 2012;125(4):620-37.
2. Bohnen MS, Peng G, Robey SH, Terrenoire C, Iyer V, Sampson KJ, et al. Molecular pathophysiology of congenital long QT syndrome. Physiol Rev. 2017;97(1):89-134.
3. Clark RB, Giles WR. Current-voltage relationship for late Na(+) current in adult rat ventricular myocytes. Curr Top Membr. 2016;78:451-78.
4. Santos-Miranda A, Cruz JS, Roman-Campos D: Electrical properties of isolated cardiomyocytes in a rat model of thiamine deficiency. Arq Bras Cardiol. 2015;104(3):242-5.
5. Santos MS, Oliveira ED, Santos-Miranda A, Cruz JS, Gondim ANS, Menezes-Filho JER, et al. Dissection of the effects of quercetin on mouse myocardium. Basic Clin Pharmacol Toxicol. 2017;120(6):550-9.
6. Iyer V, Roman-Campos D, Sampson KJ, Kang G, Fishman GI, Kass RS. Purkinje cells as sources of arrhythmias in long QT syndrome type 3. Sci Rep. 2015 Aug 20;5:13287.
7. Rosati B, Grau F, McKinnon D. Regional variation in mRNA transcript abundance within the ventricular wall. J Mol Cell Cardiol. 2006;40(2):295-302.
8. Fraser H, Belardinelli L, Wang L, Light PE, McVeigh JJ, Clanachan AS: Ranolazine decreases diastolic calcium accumulation caused by ATX-II or ischemia in rat hearts. J Mol Cell Cardiol. 2006;41(6):1031-8.
9. Allen TJ, Chapman RA. Effects of ranolazine on L-type calcium channel currents in guinea-pig single ventricular myocytes. Br J Pharmacol. 1996;118(2):249-54.
10. Honen BN, Saint DA: Heterogeneity of the properties of INa in epicardial and endocardial cells of rat ventricle. Clin Exp Pharmacol Physiol. 2002;29(3):161-6.
11. Chaitman BR, Skettino SL, Parker JO, Hanley P, Meluzin J, Kuch J, et al. Anti-ischemic effects and long-term survival during ranolazine monotherapy in patients with chronic severe angina. J Am Coll Cardiol. 2004;43(8):1375-82.

This is an open-access article distributed under the terms of the Creative Commons Attribution License

Statement

Declaration of potential conflict of interests of authors/collaborators of the Luso-Brazilian Position Statement on Hypertensive Emergencies – 2020
If, within the last 3 years, the author/collaborator of the statement:

Names of statement collaborators	Participated in clinical and/or experimental studies sponsored by pharmaceutical or equipment companies related to this guideline	Spoke at events or activities sponsored by industry related to this guideline	Was (is) a member of a board of advisors or a board of directors of a pharmaceutical or equipment industry	Participated in normative committees of scientific research sponsored by industry	Received personal or institutional funding from industry	Wrote scientific papers in journals sponsored by industry	Owns stocks in industry
Celso Amodeo	Medtronic	No	No	No	Novonordisk, Pfizer, Sankyo	Medley	No
Dilma do Socorro Moraes de Souza	No	No	No	No	No	No	No
Eduardo Costa Duarte Barbosa	No	Servier, EMS	No	No	Servier, EMS, Torrent	EMS, Medley, Novartis	No
Fernando Carvalho Moreira Pinto	No	No	No	No	No	No	No
Francisco José Torres González	No	No	No	No	No	No	No
Jorge Junqueira Polonia	No	No	No	No	No	No	No
Jose Fernando Vilela-Martin	No	No	No	No	No	No	No
Juan Carlos Yugar-Toledo	No	No	No	No	No	No	No
Luís Carlos Bronze S. Carvalho	No	No	No	No	No	No	No
Luís Filipe Reis Martins	No	No	No	No	No	No	No
Manuel de Carvalho Rodrigues	No	No	No	No	No	No	No
Marcus Vinícius Bolivar Malachias	No	Libbs, Biolab	No	No	No	Libbs, Biolab, Aché	No
Oswaldo Passarelli Júnior	No	No	No	No	No	No	No
Paulo César Veiga Jardim	No	No	No	No	No	Biolab, Aché, Libbs	No
Rui Manoel dos Santos Póvoa	No	No	No	No	No	No	No
Vitor Manuel Margarido Paixão Dias	No	No	No	No	Servier, Tecnimede	No	No
Weimar Kunz Sebba Barroso	Boehringer, Torrent, EMS, Amgen, AstraZeneca, Novartis	EMS, Servier, Medley, Omron, Cardios	Omron	No	EMS, Servier	EMS, Servier, Medley	No

Content

1. Definition, Epidemiology, and Classification of Hypertensive Emergencies

Hypertensive emergencies (HEs) comprise a wider nosological condition known as hypertensive crisis (HC). HC represents clinical situations with acute blood pressure (BP) elevation, often with levels of systolic BP (SBP) ≥ 180 mmHg and diastolic BP (DBP) ≥ 120 mmHg, which may or may not result in **target-organ damage** (TOD) (heart, brain, kidneys, and arteries).[1-5] HCs may present in two distinct forms in relation to severity and prognosis: hypertensive urgency (HU) and HE. Cases of HE have a marked elevation in BP associated with TOD and immediate risk of death, a fact that requires a rapid and gradual reduction in BP levels within minutes to hours, with intensive monitoring and use of intravenous medications.[1-5] HEs can manifest as cardiovascular, cerebrovascular, or renal events or as a pregnancy-related event in the form of preeclampsia or eclampsia. Although the classic definition of both HC presentations describes this condition with values above 180/120 mmHg, the largest current consensus is established on the concept that what distinguishes HEs from HUs is, more than the BP value, the occurrence of damage or imminent risk of target-organ involvement. Thus, HUs are characterized by BP elevations without TOD or imminent risk of death, a fact that allows for a slower reduction in BP levels over a period of 24 to 48 hours. Currently, there is a wide discussion about the actual existence of the diagnosis of "hypertensive urgency."[6] Many advocate that this classification needs to be updated (if not abandoned) and that, instead of the BP value, the main diagnostic importance lies in the observation of signs/symptoms and acute TOD. Others believe that the correct term should be "BP elevation without evolving TOD."[5,7]

As discussed, even though the BP levels are often very high (≥ 180/120 mmHg), HEs are defined by TOD and not by BP levels. Therefore, the numerical pattern that defines HC is conceptual and serves as a therapeutic parameter, but should not be used as an absolute criterion.

If the definition of HC is more universally accepted today, the knowledge about the epidemiology and prevalence of this condition by the scientific community is still limited. The literature has only a few studies on the subject, all of which conducted in a small number of participants. Non-adherence to treatment is currently hypothesized to be one of the most prevalent factors in the etiology of HC, without distinction between HU and HE. The incidence of HC in the largest serial studies in the US was about 4.8%, with 0.8% attributed to HEs.[8,9] Other centers have shown that HCs account for a variable rate of 0.45 to 0.59% of all hospital emergency care and 1.7% of all clinical emergencies, with HU being more common than HE.[10-12] Ischemic stroke and acute pulmonary edema (APE) are the most common clinical conditions in HE.[10,11] Estimates indicate that about 1% of all hypertensive individuals will probably develop an episode of HC over their lifetimes.[1,2] The clinical conditions with TOD implicated in HEs are shown in Table 1. Table 2 shows the main conditions associated with HUs.

Table 1 – Conditions with target-organ damage characterizing hypertensive emergencies[1-5]

Severe hypertension associated with acute complications
Cerebrovascular events
- Hypertensive encephalopathy
- Intracerebral hemorrhage
- Subarachnoid hemorrhage
- Ischemic stroke
Cardiocirculatory events
- Acute aortic dissection
- Acute pulmonary edema with left ventricular failure
- Acute myocardial infarction
- Unstable angina
Renal disease
- Rapidly progressive renal failure
Severe adrenergic crisis
- Pheochromocytoma crisis
- Illicit drug overdose (cocaine, crack, LSD)
Hypertension in pregnancy
- Eclampsia
- Severe preeclampsia
- "HELLP" syndrome
- Severe hypertension in late pregnancy

HELLP: hemolysis, elevated liver enzymes, and low platelet count; LSD: lysergic acid diethylamide.

Table 2 – Conditions associated with hypertensive urgency[1-5]

Severe hypertension associated with:
- Coronary insufficiency
- Cardiac insufficiency
- Aortic aneurysm
- Uncomplicated stroke
- Severe epistaxis
- Extensive burns
- Hypocoagulability states
Systemic vasculitis
- Perioperative
- Preoperative in emergency surgeries
- Intraoperative (cardiac surgery, vascular surgery, neurosurgery, pheochromocytoma, etc.)
- Postoperative stage III hypertension (organ transplantation, cardiac surgery, vascular surgery, neurosurgery, etc.)
Mild/moderate adrenergic crisis
- Rebound syndrome (abrupt discontinuation of adrenergic inhibitors)
- Drug-food interaction (tyramine vs. MAO inhibitors)
- Excessive use of stimulants (amphetamines, tricyclics, etc.)
In pregnancy
- Preeclampsia
- Stage III hypertension

MAO: monoamine oxidase.

2. Pathophysiological Aspects of Hypertensive Emergency

The pathophysiology of HE has not been completely elucidated, and in general, two different mechanisms may play central roles in this process. The first is an imbalance in the vascular autoregulation system leading to reduced perfusion pressure and, consequently, decreased blood flow and increased vascular resistance, resulting in mechanical stress and endothelial injury.[13] The second mechanism is an activation of the renin-angiotensin system resulting in greater vasoconstriction and leading to a vicious cycle of endothelial injury, fibrinoid necrosis of arterioles, and subsequent ischemia.[14] Vascular injury leads to platelet and fibrin deposition, also characterizing a prothrombotic state.[15] Subsequent ischemia results in the release of more vasoactive substances, creating a vicious cycle.

2.1. Autoregulation of Cerebral Blood Flow

Knowledge about the mechanism of autoregulation of blood flow to target organs (brain, coronary arteries, and kidneys) is fundamental for improved antihypertensive treatment in cases of HE. Autoregulation of cerebral blood flow (CBF) is maintained by the ratio of cerebral perfusion pressure (CPP) to cerebrovascular resistance (CVR), *i.e.*, CBF = CPP/CVR (CPP = mean BP - mean venous pressure). CPP is the difference between BP – which helps with tissue blood flow – and venous pressure. With a normal CPP, venous pressure is not important, so CPP is equivalent to BP. Reductions in CPP may be caused by reductions in BP or increased intracranial pressure (ICP), which increases venous pressure. Elevations in ICP may occur as a result of arterial or venous occlusive disease or intracerebral hemorrhage. In normotensive individuals, a wide variation in BP (between 60 and 150 mmHg) may occur without CBF changes. An increase in CPP (or BP) leads to an elevation in CVR, thus protecting the patient against cerebral edema, while reductions in CPP result in decreased CVR, thus protecting the patient from tissue ischemia. When CPP exceeds the upper limit of autoregulation, CBF increases, causing cerebral edema. In contrast, when CPP falls below the lower limit of autoregulation, CBF decreases, causing cerebral ischemia.[16,17]

In hypertensive individuals, this relationship is modified in a way that their lower limit of autoregulation is higher compared with normotensive individuals. Thus, improper decrease in CPP can hinder tissue irrigation and, consequently, aggravate the viable ischemic area. For this reason, it is advisable to initially reduce the mean BP by 20 to 25% in relation to the initial values, as this will bring them close to the lower autoregulation limit.[18] Attention should be given to this situation, as most patients with HE have chronic

hypertension with the pressure/flow (cerebral, coronary, and renal) autoregulation curve shifted to the right and do not present acute TOD, which is why a sudden decrease in BP may be associated with significant morbidity.[18-20]

3. Clinical and Laboratory Assessment

When managing a HE, the practitioner should discriminate between emergency and urgency, establishing a correct diagnosis of the various HE situations in order to select the most appropriate therapy for each TOD. This is very important since the correct diagnosis and treatment may prevent worsening of the clinical condition due to the critical situation. The approach to patients with HE requires clinical evaluation and complementary tests performed in clinical emergency centers with hospital support. BP should be measured in both arms (at least three measurements), preferably in a quiet environment. Individuals with acute BP elevations often present metabolic abnormalities characterized by hyperglycemia, dyslipidemia, lower potassium levels, and reduced renal function.[21] The sequence of steps in the management of patients with HC is as follows:[1-5,22,23]

1. Seek factors that may have triggered the acute BP elevation.
2. Investigate symptoms or situations that simulate HC (headache, labyrinthitis, physical trauma, pain, emotional stress, and family or professional problems).
3. Observe history and duration of hypertension, use of antihypertensive drugs (doses and pharmacological adherence).
4. Investigate prior episodes similar to the current situation.
5. Investigate the use of medications that may interfere with BP control (anti-inflammatory drugs, steroids, analgesics, antidepressants, appetite suppressants).
6. Evaluate the use or abuse of alcohol and toxic substances (cocaine, crack, lysergic acid diethylamide [LSD]).
7. Investigate the use of suddenly discontinued adrenergic inhibitors (clonidine, methyldopa, and beta-blockers).
8. Observe the association with other morbidities and risk factors (diabetes, cardiac disease, renal disease, smoking, dyslipidemia).
9. Clinical history and physical examination should be performed according to the presence of TOD:
   - Central nervous system (observe the occurrence of headache, dizziness, visual and speech disorders, consciousness level, agitation or apathy, confusion, focal neurological deficits, neck stiffness, seizure, and coma).
   - Cardiovascular system (assess heart rate, symptoms of palpitations, and presence of carotid murmur; investigate the occurrence of thoracic, precordial, abdominal, and back pain and discomfort, in addition to signs and symptoms of left ventricular failure including gallop rhythm, dyspnea, jugular venous stasis, peripheral pulses, and oxygen saturation).
   - Renal and genitourinary system (assess changes in urinary volume, frequency, and characteristics, dehydration, lower limb edema, hematuria, and dysuria). Note: examination of the abdomen (for pulsatile abdominal masses and abdominal murmur) should not be overlooked.
   - Fundoscopy (observe the occurrence of vasospasm, arteriovenous nicking, arteriolar wall thickening and aspect of copper or silver-wiring, hard and soft exudates, hemorrhages, and papilledema).

Complementary tests should be performed according to the involvement of target organs:

- Central nervous system (computed tomography, magnetic resonance imaging, and lumbar puncture).
- Cardiovascular system (electrocardiography, chest x-ray, echocardiography, markers of myocardial necrosis, angiotomography, magnetic resonance imaging).
- Renal system (urinalysis, urea, creatinine, electrolytes, and blood gases).

4. Treatment of Hypertensive Emergencies: General Principles, Main Medications and Dosages

Better diagnostic and therapeutic conditions have led to a great reduction in 1-year mortality, which improved from 80% in 1928 and 50% in 1955 to only 10% in 1989.[24,25] The aim of treating patients with clinical manifestations of HE is to reduce BP rapidly to prevent the progression of TOD. Patients should be admitted to an intensive care unit, undergo intravenous antihypertensive treatment, and be carefully monitored during parenteral therapy to prevent the occurrence of hypotension. The general recommendations for BP reduction suggested by the Seventh Report of the Joint National Committee (JNC)[26] for HEs are summarized as follows:

- ↓ BP ≤ 25% within the first hour.
- ↓ BP 160/100 to 110 mmHg in 2 to 6 hours.
- BP 135/85 mmHg at 24 to 48 hours.

However, HEs should be addressed considering the affected system or target organ. Thus, each type of HE (cardiovascular, cerebral, renal, and others) should be characterized prior to starting specific antihypertensive therapy (see "Clinical and Laboratory Evaluation").

Several pharmacological therapies are currently available for HE treatment. The ideal antihypertensive medication for parenteral use must present the following characteristics: ability to reverse the involved pathophysiological abnormalities, rapid onset of action, predictable dose-response curve, minimal dose adjustment, high selectivity, no increase in ICP, prompt reversibility, low risk of promoting hypotension, easy substitution for oral medications, and satisfactory cost-benefit ratio. Table 3 summarizes the pharmacokinetic and pharmacodynamic properties of the main antihypertensive medications used in HE.[2,22,26-28] In Brazil, the following medications are available for use in HEs: sodium nitroprusside, nitroglycerin, labetalol, esmolol, metoprolol, hydralazine, and enalaprilat.

Table 3 – Pharmacokinetic and pharmacodynamic properties of the main antihypertensive medications for parenteral use

Medications	Method of administration and dosage	Start	Duration	Advantages	Disadvantages
Nitroglycerin (nitric oxide donor with arterial and venous vasodilation effects)	Continuous infusion 5 to 15 mg/h	2 to 5 min	3 to 5 min	Coronary perfusion	Headache, variable efficacy, tachyphylaxis
Sodium nitroprusside (arterial and venous vasodilator)	Continuous infusion 0.5 to 10 µg/kg/min	Immediate	1 to 2 min	Titration	Intoxication by thiocyanate, hypotension, nausea, vomiting, muscle spasm
Metoprolol (beta-blocker)	Loading dose: 5 mg IV (repeat every 10 min, up to 20 mg if necessary)	5 to 10 min	3 to 4 h	Reduction in O_2 consumption	Bradycardia, AVB, bronchospasm
Labetalol (alpha- and beta-blocker)	Loading dose: 20 to 80 mg every 10 min Continuous infusion 2 mg/min (maximum 300 mg/24 h)	5 to 10 min	2 to 6 h	Beta-blocker and vasodilator	Nausea, vomiting, AVB, bronchospasm, orthostatic hypotension
Esmolol (Ultra-fast action, ultra-selective beta-blocker)	Loading dose: 500 µg/kg Intermittent infusion: 25 to 50 µg/kg/min ↑ 25 µg/kg/min every 10 to 20 min. Maximum: 300 µg/kg/min	1 to 2 min	1 to 20 min	Selective beta-blocker	Bradycardia, AVB, bronchospasm
Hydralazine (direct-acting vasodilator)	10 to 20 mg IV or 10 to 40 mg IM every 6 h	10 to 20 min IV or 20 to 30 min IM	3 to 12 h	Eclampsia or impending eclampsia	Tachycardia, headache, vomiting. Worsening of angina and AMI. Beware of increased intracranial pressure
Enalaprilat (ACEI)	Intermittent infusion: 1.25 to 5 mg every 6 h	15 min	4 to 6 h	CHF, acute LVF	Hypotension, renal insufficiency
Furosemide (loop diuretic)	Infusion	5 to 10 min	30 to 90 min	CHF, LVF	Hypokalemia

AMI: acute myocardial infarction; CHF: congestive heart failure; LVF: left ventricular failure; AVB: atrioventricular block; ACEI: angiotensin-converting enzyme inhibitor; IV: intravenous; IM: intramuscular.

5. Hypertensive Encephalopathy

Hypertensive encephalopathy is a neurological dysfunction defined by signs and/or symptoms of cerebral edema secondary to sudden and/or sustained BP elevation. It occurs in individuals with chronic hypertension who develop malignant hypertension or in those previously normotensive who may present acute BP elevations due to other mechanisms, progressing with failure in mechanisms of cerebral perfusion autoregulation. Hypertensive encephalopathy is a diagnosis of exclusion confirmed retrospectively when the neurological condition improves after BP control.

5.1. Clinical Manifestations

Hypertensive encephalopathy may present with the insidious onset of holocranial headache, nausea, or vomiting. Subsequently, changes in mental status and visual field, photopsia, blurred vision, visual hallucinations, generalized seizures, hyperreflexia, and signs of intracranial hypertension may develop.[29,30] By the time the neurological manifestations emerge, the DBP is usually above 125 mmHg. The resolution of this condition, from both clinical and imaging standpoints, occurs on average several weeks after BP control. The occurrence of a persistent deficit is a sign of focal neurological injury.

5.2. Diagnosis

Magnetic resonance imaging is the most valuable diagnostic test. T2-weighted sequences show hyperintense white matter lesions with preferential involvement of the parieto-occipital regions. The territory irrigated by the vertebrobasilar system can be compromised in more severe cases. Hyperintense signal in apparent diffusion coefficient allows for the visualization of vasogenic edema.[31] Laboratory tests may show thrombocytopenia, microangiopathic hemolytic anemia, proteinuria, and increased plasma creatinine and liver enzymes. On computed tomography, focal or diffuse hypodensities in the white matter and cortex are common, along with signs of edema. Electroencephalography shows generalized slowing with loss of alpha rhythm, or epileptiform activity if seizures occur.

5.3. Treatment

The goal is to reduce the average BP by approximately 10 to 15% in the first hour and by no more than 25% at

the end of the first day of treatment. Greater and faster decreases may lead to cerebral hypoperfusion and loss of vascular autoregulation mechanisms.[32,33] Due to the need for rapid BP control, intravenous medications are recommended, of which the most frequently used are sodium nitroprusside (arterial and venous vasodilator), nicardipine (dihydropyridine calcium-channel blocker with arteriolar vasodilation action), clevidipine (short-acting dihydropyridine calcium-channel blocker), labetalol (alpha-adrenergic and beta-adrenergic blocker), or fenoldopam (peripheral dopamine-1 receptor agonist). During pregnancy, magnesium sulfate, diazoxide, or hydralazine are recommended. Corticosteroids (dexamethasone), mannitol (may be used in the absence of renal disease), and anticonvulsants (in case of seizures) may also be used.[23,30] Within the first 24 to 48 hours, oral medications should be introduced to improve BP control (renin-angiotensin-aldosterone system blockers and calcium-channel blockers), with a gradual DBP reduction to values below 90 mmHg in the following 2 to 3 months.[1,2,5,22]

6. Malignant or Accelerated Hypertension

Malignant hypertension is characterized by hypertension at varying levels, but usually very high BP (stage 3), retinopathy with papilledema, and rapidly progressive TOD (kidneys and heart), with a fatal outcome in the absence of therapeutic intervention (Figure 1). Severe BP elevation in the presence of retinal hemorrhages and exudates but no papilledema on fundoscopy is known as accelerated hypertension (Figure 2). After demonstration that the clinical findings and prognosis of these two forms of hypertension are similar,[34] the terms "malignant" and "accelerated" became interchangeable, and the World Health Organization currently uses the term accelerated-malignant to define this complication. Characteristically, malignant hypertension presents with systemic vascular changes affecting particularly the kidneys (known as malignant nephrosclerosis) and involving basically two processes: (a) proliferative endarteritis affecting small and large arterioles with intimal thickening, fragmentation, and reduplication of the internal elastic lamina and smooth muscle proliferation; the progression of this lesion, which resembles an "onion skin," may lead to occlusion of the vessel lumen with consequent reduction in renal blood flow; (b) necrotizing changes in arterioles, especially in the glomerular hilum, and vessel wall reconstruction with eosinophilic granular material that exhibits the characteristics of fibrin (fibrinoid necrosis), causing destruction of the normal morphology and deep lumen narrowing. These changes may occur in organs other than the kidneys and are primarily responsible for the fatal complications of the disease (Figure 3).[35] The prognosis of malignant hypertension is almost always fatal if not early recognized or properly treated; in the past, the associated mortality reached 80% within 2 years.[36] However, since the introduction of antihypertensive treatment, studies have shown that the survival of individuals with malignant hypertension has improved substantially.[37-39] In a publication including almost 500 patients in Birmingham (United Kingdom), the authors reported a significant improvement in 5-year survival from 32% before 1977 to 91% in patients diagnosed between 1997 and 2006.[38] Management of patients with malignant hypertension usually includes the use of four classes of drugs, and hypertensive complications may stabilize and, in some cases, even be reversed.

7. Stroke and Hypertensive Emergency

Stroke may present as a HE. Individuals with chronic hypertension present a right shift in the autoregulation curve for CBF causing them to tolerate substantially higher BP values without developing encephalopathy. Patients with chronic hypertension who have their BP values aggressively and rapidly reduced may present symptoms of cerebral hypoperfusion, even when the values are within the autoregulation range, as observed in normotensive individuals. Finally, patients with severe hypertension may lose the ability of autoregulation, thus presenting an increased risk of cerebral ischemia with abrupt BP reductions.[16-18]

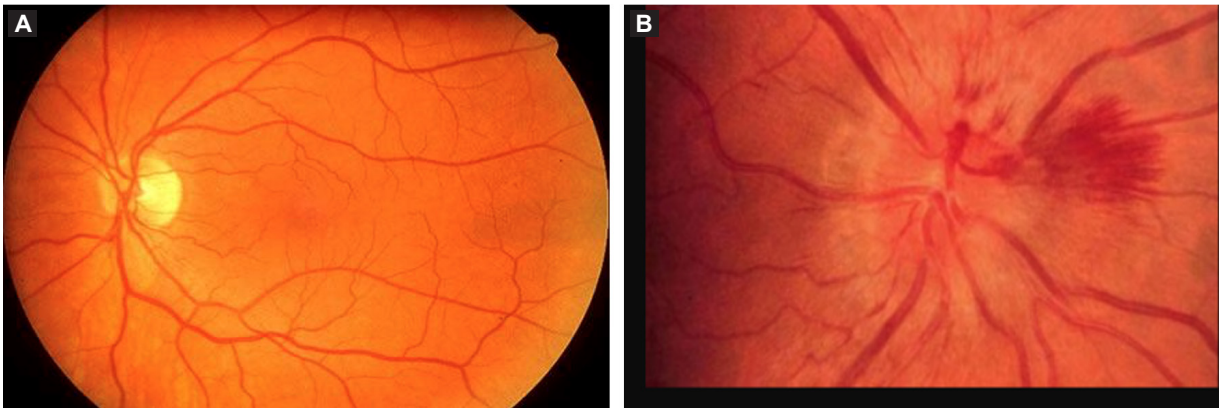


Figure 1 – *Normal fundoscopy (A). Fundoscopy of an individual with malignant hypertension and papilledema (B).*

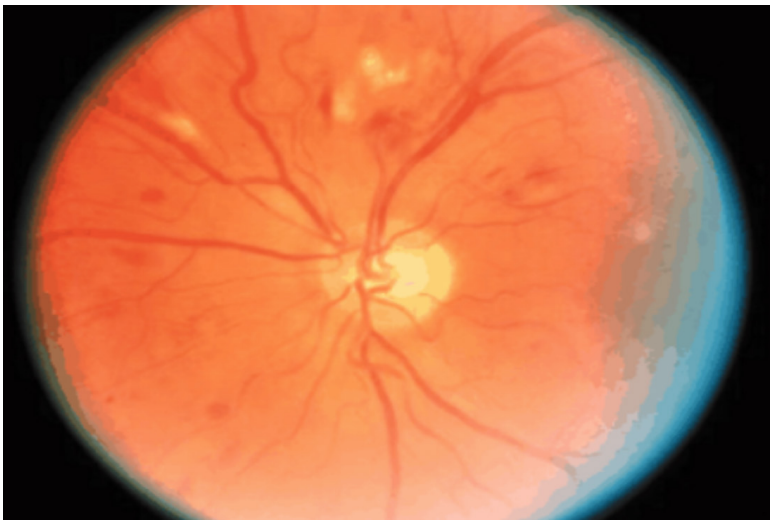


Figure 2 – *Fundoscopy showing normal papillae, diffuse arteriolar narrowing, areas with superficial hemorrhage, and microaneurysms (grade III hypertensive retinopathy according to the Keith-Wagener classification).*

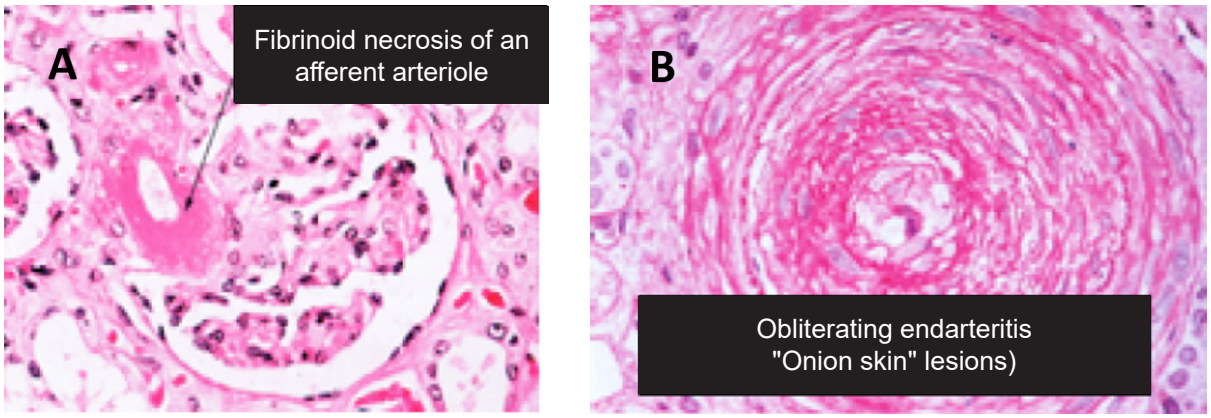


Figure 3 – *Anatomopathological lesions typical of accelerated-malignant hypertension. Fibrinoid necrosis of an afferent arteriole (arrow) (A). Obliterating endarteritis ("onion skin" lesions) (B).*

7.1. Ischemic Stroke

In ischemic stroke, careful BP reductions of 10 to 15% are recommended at the end of the first hour after initiation of therapy and only if SBP is > 220 mmHg or DBP is > 120 mmHg.[40] If SBP is > 180 to 230 mmHg or DBP is > 105 to 120 mmHg and the patient is not undergoing thrombolysis, the following therapy is recommended: intravenous labetalol 10 mg followed by continuous infusion at a dose of 2 to 8 mg/min; or nicardipine at the cited doses until the desired effect is obtained. If uncontrolled BP or DBP > 140 mmHg persists, intravenous sodium nitroprusside should be considered.[40]

In the case of individuals with elevated BP and indication for thrombolytic therapy with alteplase, BP should be carefully reduced until SBP < 185 mmHg and DBP < 110 mmHg before administration of the thrombolytic. If BP remains above 185/110 mmHg, thrombolytic therapy should not be administered.[40] Labetalol is the first medication of choice, and nicardipine is the alternative therapy. A dose of intravenous labetalol of 10 to 20 mg is recommended for 1 to 2 minutes (may be repeated once). Nicardipine is recommended at the dose of 5 mg/h and administered intravenously, with dose titration of 2.5 mg/h every 5 to 15 minutes (maximum dose of 15 mg/h). During or after

thrombolysis or other reperfusion therapy, BP should be maintained at or below 180/105 mmHg.[40]

7.2. Hemorrhagic Stroke

Treatment goals in hemorrhagic stroke are controversial.[41-43] Elevation in BP is common during acute intracerebral hemorrhage and is associated with a higher risk of expansion of the hematoma, increased risk of death, and worse recovery prognosis. In this case, immediate (within 6 hours) decrease in BP to values < 140/90 mmHg has shown no benefit in the primary outcome of disability or death at 3 months, despite reducing the expansion of the hematoma and improving functional recovery.[41] In contrast, another study has shown that a more intensive reduction in SBP is not beneficial and is associated with a greater number of adverse renal events.[42] Thus, in individuals with hemorrhagic stroke, European guidelines recommend against immediate BP reduction for patients with SBP < 220 mmHg.[44] In individuals with SBP ≥ 220 mmHg, careful BP reduction with intravenous therapy to achieve SBP < 180 mmHg should be considered[44]. Labetalol, at the aforementioned doses, is the first therapeutic choice, and sodium nitroprusside and nicardipine are the alternative therapies.[1-4,28]

8. Acute Coronary Syndromes and Hypertensive Emergency

Epidemiological data indicate that acute coronary syndrome (ACS) is the leading cause of death and hospitalization in patients with HE. Additionally, almost 50% of all patients with hypertension admitted to the emergency room die of acute myocardial infarction (AMI) during long-term follow-up. Notably, no differences have been found when other risk factors are present, such as smoking or diabetes mellitus.[11,45] Obviously, hypertension is associated with acute coronary events as a risk, atherogenic, and hemodynamic factor, imposing profound effects on cardiovascular morbidity and mortality. During a HE, increased BP causes mechanical stress and endothelial injury, leading to increased vascular permeability, activation of the coagulation cascade and platelets, fibrin deposition, and thrombosis. This process results in ischemia and release of vasoactive mediators, leading to a vicious cycle of permanent injury. The activation of the renin-angiotensin system leads to increased vasoconstriction and production of proinflammatory cytokines (tumor necrosis factor [TNF]-alpha, interleukin [IL]-6, etc.). It also increases NADPH oxidase activity and production of reactive oxygen species, causing oxidative stress. These mechanisms promote hypoperfusion, myocardial ischemia, and endothelial dysfunction, which manifest during the HE.[14,15]

Assessment of cardiovascular risk and investigation of comorbidities are essential in the approach to patients presenting with HE and ACS. Electrocardiography is the gold standard for the detection of ischemia or acute coronary events. Also, vital signs (BP, oxygen saturation, and heart rate) should be carefully measured during physical examination in patients with HE. Laboratory analysis includes the quantification of cardiac enzymes and determination of troponin I. In a retrospective study, patients with HC and increased cardiac troponin I (cTn-I) concentration were 2.7 times more likely to present adverse cardiovascular events and stroke at 2 years of follow-up compared with those with normal cTn-I values.[46]

Treatment of HE associated with ACS should initiate with nitroglycerin infusion. Nitroglycerin is a venodilator that reduces preload and cardiac oxygen demand. This agent is used mainly in ACS and acute edema along with other antihypertensive regimens.[47-49] An alternative to nitroglycerin intolerance is the administration of dihydropyridine calcium-channel blockers (amlodipine, nicardipine), as they are useful for patients with ACS because of their beneficial effect on coronary blood flow. Alternatively, clevidipine – a short-acting calcium-channel blocker – may be administered intravenously, and since its dosing regimen is not based on weight, it allows for prolonged infusion and successful transition to oral therapy.[50] If available, especially in ST-segment elevation ACS, primary angioplasty is the best choice for reperfusion therapy in patients with HE, as thrombolysis may increase the risk of cerebral bleeding.[47-49,51]

Beta-blockers like labetalol (a nonselective alpha-1-adrenergic receptor blocker), which reduces systemic vascular resistance while maintaining cerebral, renal, and coronary blood flow, or esmolol (a short-acting cardioselective beta-1 blocker with fast onset of action) are indicated to attenuate the increase in heart rate, reduce myocardial oxygen consumption without compromising the left ventricular diastolic filling, and improve prognosis.[28] Additionally, BP reduction decreases the risk of pulmonary edema and the size of the infarct zone.[52] Tolerance to higher maintenance doses of esmolol is a good predictor of results with oral beta-blocker therapy.[53]

The optimal BP value after ACS remains controversial. Several studies have shown an inverse relationship between DBP and ischemic adverse cardiac events (*i.e.*, the lower the DBP, the higher the risk of coronary heart disease and adverse outcomes). This effect is defined as the J-curve phenomenon, which describes the shape of the relationship between BP and the risk of cardiovascular morbidity and mortality.[54] This profile seems to be more pronounced in patients with underlying coronary artery disease.[55]

9. Acute Left Ventricular Dysfunction in Hypertensive Emergency

Acute left ventricular dysfunction is best known as APE. HE, acute mitral regurgitation (papillary muscle dysfunction secondary to ischemic disease or spontaneous rupture), and ACS are the most common causal factors of cardiogenic APE.[56,57] About 1/3 of the patients admitted with APE and HE have preserved left ventricular function. Patients with HE presenting manifestations of APE should be managed in an intensive care unit, receive parenteral medications and monitoring, and undergo gradual BP decrease.[58] Nitroglycerin and sodium nitroprusside are used to reduce preload and afterload. Administration of loop diuretics also decreases volume overload and helps reduce BP. The use of noninvasive continuous positive airway pressure may help reduce pulmonary edema and venous return.[28,59]

10. Acute Aortic Syndromes

Acute aortic syndrome (AAS), a term currently comprising aortic dissection (AD), intramural hematoma (IMH), and penetrating atherosclerotic ulcerations (PAU), has an incidence that ranges from 3.5 to 6.0 per 100,000 patients/year.[60] Given its high mortality rate, AAS should be considered and promptly diagnosed in patients with acute chest or back pain, especially if associated with hypertension. Computed tomography, magnetic resonance imaging, and transesophageal echocardiography are reliable imaging tests to diagnose AAS, while measurement of serum D-dimer has shown 51.7 to 100% sensitivity and 32.8 to 89.2% specificity in six studies.[61]

Of all AAS types, AD is the most common (85 to 95%), followed by IMH (0 to 25%) and PAU (2 to 7%).[61] According to the Stanford classification, AAS is divided into type A, which involves the ascending aorta, and type B, which does not involve this segment. In contrast, the DeBakey classification divides AAS into type I, which involves at least the ascending aorta and the aortic arch and often also the descending aorta; type II, which is confined to the ascending aorta; and type III, which originates in the distal descending aorta and affects the left subclavian artery.[60] AAS may be associated with several risk factors including the male sex, advanced age, first-degree relatives with a history of AAS, hypertension, dyslipidemia, smoking, illicit drug use, history of major vascular arteritis (*e.g.*, Takayasu arteritis), collagen vascular disease (like Marfan's, Loeys-Dietz, and Ehlers-Danlos syndrome), blunt trauma from motor vehicle accident or vertical fall, arterial instrumentation for diagnostic or therapeutic purposes, or hereditary mutations in genes encoding proteins involved with vascular integrity (such as mutation in the *ACTA2* gene).[60]

10.1. Treatment

Treatment of AAS requires a multidisciplinary approach involving clinical, endovascular, and surgical interventions.[62] Type A ADs have a poor prognosis and an overall in-hospital mortality of 30%, with a mortality increase of 1 to 2% per hour of progression.[63] Without intervention, the mortality is about 58%, compared with 26% with surgical intervention.[63] Open surgery is the ideal treatment for type A AAS (ascending aorta), and thoracic endovascular aortic repair is best suited to treat type B AAS (descending aorta).[64-66] Endovascular surgery has been shown to be better than medical treatment (97% *vs.* 43%) considering the favorable aortic remodeling, false lumen thrombosis, and absence of aortic dilation or rupture.[66]

Initial management of AD involves pain control and use of antihypertensive agents. Intravenous beta-blockers (metoprolol, esmolol, or labetalol) should be administered to reduce wall stress, lowering heart rate and BP and maintaining adequate cerebral, coronary, and renal perfusion.[60] Administration of beta-blockers should be completed before BP reduction with afterload reducing agents. Guidelines recommend a SBP reduction to 100 to 120 mmHg and a heart rate below 60 bpm.[65] In case of intolerance to beta-blockers, non-dihydropyridine calcium-channel blockers (verapamil or diltiazem) should be used.[67] After proper beta blockade, afterload should be reduced. Although angiotensin-converting enzyme inhibitors (ACEIs) have not shown significant benefits in terms of mortality, they have been used as adjuvant agents to reduce BP.[68] Sodium nitroprusside may also be used after beta blockade since, as monotherapy, this agent may increase shear stress of the aortic wall resulting in progression of the dissection.[60] To date, there is no known indication for early platelet blockade in AD control.[60] Several studies have shown that the use of statins reduces the growth rate of abdominal aortic aneurysm (AAA) and decreases the likelihood of recurrent rupture after repair.[69] Still, the role of statins in AAS is unclear.[69] Effective pain management with morphine sulfate, fentanyl, or opiate should be implemented.[60]

11. Hypertensive Emergencies During Pregnancy

Hypertension is the most common medical problem in pregnancy, manifesting in up to 10% of all pregnancies and accounting for about 25% of prenatal hospital admissions; it is also an important cause of maternal and fetal morbidity and mortality. Women with hypertension during pregnancy are at higher risk for future hypertensive disease, stroke, and coronary artery disease.[70,71] The definition of hypertension in pregnancy follows the same criteria of the Brazilian Guideline of Arterial Hypertension, i.e., BP ≥ 140/90 mmHg. Hypertension during pregnancy is considered severe when SBP values are ≥ 160 to 170 mmHg and DBP are ≥ 110 mmHg.[72] Thus, hypertension may precede (in this case, chronic hypertension) or develop during the course of pregnancy (preeclampsia/eclampsia/gestational hypertension), characterizing four different categories of hypertension:[70-72]

1. Chronic hypertension begins before pregnancy or is diagnosed before the 20th week of gestation. Only 20 to 25% of the cases of chronic hypertension in pregnancy progress to preeclampsia.
2. Gestational hypertension is the most common disorder (10% of the cases occur in primiparous women; 20 to 25% of the cases overlap chronic hypertension). It develops after the 20th gestational week and is not accompanied by proteinuria. BP returns to normal values 1 to 2 weeks after delivery. Progresses with a favorable maternal and fetal prognosis.
3. Preeclampsia/eclampsia. Preeclampsia (PE), a process specific of pregnancy, is defined by hypertension that appears after the 20th gestational week and presents with proteinuria (> 300 mg/24 hours or protein/creatinine ratio > 300 mg/g), edema, and sometimes abnormal coagulation and liver function. Preeclampsia can progress rapidly to eclampsia, a clinical condition characterized by tonic-clonic seizures preceded by severe hypertension, headache, and hyperreflexia. Cerebral hemorrhage is the most serious complication, with a high rate of maternal mortality. Proteinuria and elevated BP should return to normal within 12 weeks after delivery.
4. Chronic hypertension with preeclampsia/overlapping eclampsia. This condition should be suspected in the presence of microalbuminuria (30 to 300 mg in 24-hour urine or 30 to 300 mg/g albumin/creatinine ratio in spot

urine), increase in preexisting proteinuria, clinical or laboratory abnormality characteristic of preeclampsia, or elevation in preexisting BP levels after the 20th gestational week in a patient with chronic hypertension.

11.1. Treatment

The two main key points in the treatment of HC in pregnancy are (1) stabilization of the mother, including the use of antihypertensive medications that are safe and appropriate for use in pregnancy, and delivery recommendation; and (2) fetal well-being, which must be confirmed by fetal monitoring and ultrasound.

Pharmacological treatment should be initiated at BP levels > 150/100 mmHg, aiming at maintaining the levels at 130 to 150/80 to 100 mmHg (degree of recommendation [DR]: IIa; level of evidence [LE]: B). In patients with preeclampsia in stable clinical condition without the need for immediate delivery, oral antihypertensive treatment is indicated.[72] In Brazil, the oral medications that are usually administered are methyldopa, hydralazine, calcium-channel antagonists (long-acting nifedipine, amlodipine), and beta-blockers (preferably pindolol). Pregnant women with chronic hypertension may continue the use of thiazides, as long as they do not promote volume depletion.[73] The use of renin-angiotensin system blockers is contraindicated in pregnancy (DR: I; LE: B).[72]

Urgent pharmacological treatment is indicated in severe hypertension (SBP > 155 to 160 mmHg) and in the presence of premonitory signs (DR: I; LE: B). Intravenous hydralazine is recommended (5 mg, repeat 5 to 10 mg every 30 minutes to a maximum of 20 mg). Sodium nitroprusside may be considered for urgent BP control, especially in the presence of APE and severe and refractory hypertension.[72]

Magnesium sulfate is the medication of choice for both treatment and prevention of seizures during eclampsia. The patient should be monitored in terms of urine output, patellar reflexes, respiratory rate, and oxygen saturation. Plasma magnesium should be maintained between 4 and 7 mEq/L and measured in the occurrence of renal disease. If magnesium sulfate intoxication is suspected, calcium gluconate should be administered.[70,71]

12. Adrenergic Emergencies

Neuroendocrine tumors associated with sympathetic tissue with the potential to secrete catecholamines are rare and include pheochromocytomas (adrenal medulla) and paragangliomas (non-adrenal tissue). Diagnosis, location, and anatomical delineation of these tumors involve measurement of catecholamines and their metabolites in blood and urine, computed tomography and/or magnetic resonance imaging, and metaiodobenzylguanidine (I^{123}) scintigraphy. Symptoms may occur at any stage of life, are nonspecific, and depend on the release of catecholamines into the bloodstream; BP elevation, palpitations, and headache may occur. Surgical removal of these tumors is always indicated to cure or prevent cardiovascular disease secondary to catecholamine excess.[74] BP in these patients may be sustained or paroxysmal, and a marked increase in BP may characterize an impending life-threatening HE. This occurs by activation of alpha receptors by catecholamines. The Brazilian Guideline on Hypertension recommends a diagnostic flowchart for neuroendocrine tumors (pheochromocytoma and paragangliomas), which is shown in Table 4.[75] Figure 4 shows the imaging methods used for diagnostic confirmation in the occurrence of an abnormal biochemical test.

Whole-body scintigraphy is obtained to identify the location of extra-adrenal neuroendocrine tumors (paragangliomas). This test is recommended in cases of abnormal biochemical tests and negative imaging tests. It should always be performed after verification and discontinuation of medications that may interfere with their interpretation (sympathomimetics, calcium-channel blockers, cocaine, antidepressants, and labetalol), which should be suspended 14 days prior to the test. Whole-body scintigraphy is contraindicated during pregnancy.[76] After a diagnosis of neuroendocrine tumor, the proposed treatment is always surgical, preceded by pharmacological preparation and hydration to prevent or mitigate the occurrence of HC or hypotension during surgery (Table 5).[76] In this situation, intravenous antihypertensive medications are administered (initially alpha-blockers and later beta-blockers). Continuous infusion of sodium nitroprusside (0.25 to 10 mg/kg/min) or phentolamine (continuous infusion of 1 to 5 mg with a maximum dose of 15 mg) may be used with markedly increased BP.[75-77]

13. Illicit Drugs and Hypertensive Emergency

In the emergency room, patients with HC and sympathetic hyperactivity should raise suspicion of amphetamine or cocaine intoxication, as well as abusive use of other drugs like serotonin reuptake inhibitors, monoamine oxidase inhibitors, and use of cytotoxic or antiangiogenic medications.[52]

Cocaine has multiple cardiovascular and hematological effects that contribute to BP elevation, development of myocardial ischemia, and/or AMI due to coronary vasoconstriction. Cocaine, even in small doses, blocks norepinephrine and dopamine reuptake in presynaptic adrenergic terminals, causing catecholamine accumulation in the postsynaptic receptor, thus acting as a powerful sympathomimetic agent.[78] As a result, cocaine causes a dose-dependent increase in heart rate and BP.[79] In addition, cocaine use may reduce left ventricular function associated with increased parietal stress at the end of systole and increased oxygen demand. The chronotropic effects of

Table 4 – Flowchart from the 7th Brazilian Guideline of Arterial Hypertension for clinical and laboratory diagnosis of cases of pheochromocytoma and paraganglioma

Clinical findings	Suspected diagnosis	Additional studies
- Paroxysmal hypertension with headache, sweating, and palpitations - Resistant hypertension	Pheochromocytoma	- Free plasma metanephrines - Urinary metanephrines and serum catecholamines - Imaging tests

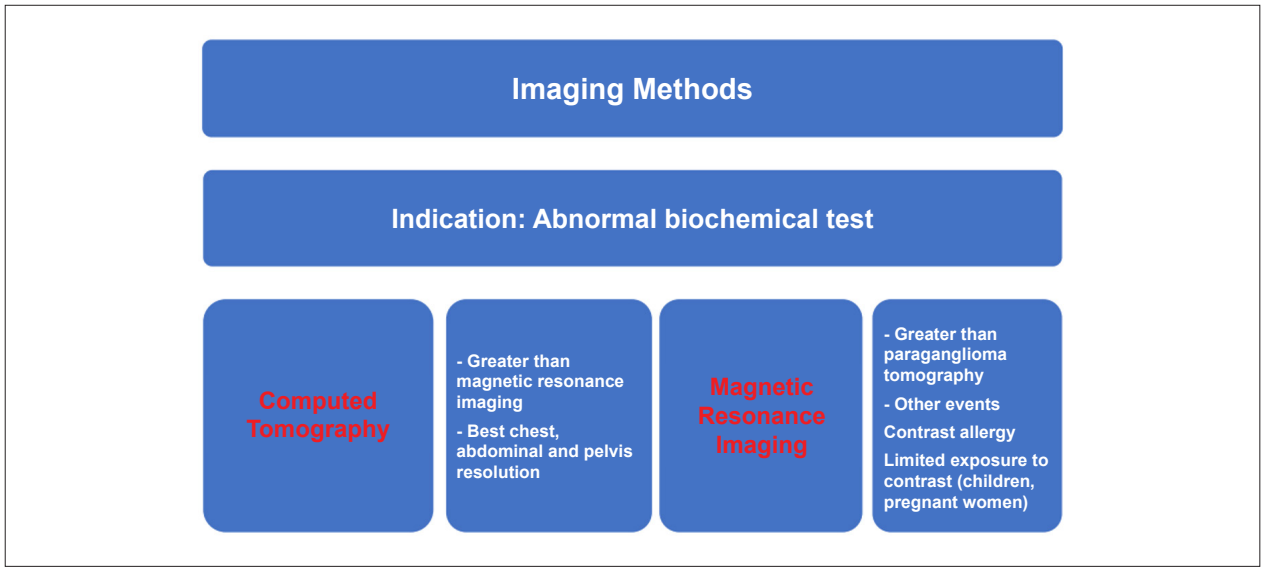


Figure 4 – *Imaging methods for diagnostic confirmation of pheochromocytoma.*

Table 5 – Preoperative care in cases of pheochromocytoma

High-sodium diet and hydration (lacks evidence):
- Saline infusion during surgery (1 to 2 L)
- Revert volume contraction
- Prevent hypotension
Pharmacological preparation:
- Alpha-adrenergic blockade
- Beta-blockers
- Calcium-channel blockers
- No evidence regarding target blood pressure
Laparoscopic adrenalectomy (most cases):
- For paragangliomas (minority)
Open adrenalectomy (for paragangliomas):
- For pheochromocytoma (minority)

cocaine use are intensified by alcohol consumption.[80] Cocaine-induced vasoconstriction is secondary to stimulation of alpha-adrenergic receptors in the smooth muscle cells of the coronary circulation. This drug also increases the release of endothelin-1[81] and decreases the bioavailability of nitric oxide, promoting BP elevation.[82] Treatment with benzodiazepines is initially indicated. When BP reduction is required, a competitive intravenous alpha-blocker agent is indicated (phentolamine). Alternatively, nicardipine or sodium nitroprusside may be considered.[83] Clonidine may also be considered because of its sedative effect in addition to sympatholytic action.

In ACS, treatment with nitroglycerin and aspirin is recommended concomitantly with benzodiazepines. In the presence of ACS with tachyarrhythmias, non-dihydropyridine calcium-channel blockers (diltiazem and verapamil) are recommended. Beta-blockers (including labetalol) are contraindicated since these agents are unable to reduce the coronary vasoconstriction.[84] Nicardipine may also be a good alternative for patients with HE induced by cytotoxic or antiangiogenic drugs.

14. Postoperative Hypertensive Emergency Following Vascular Surgery

The concept of "postoperative hypertensive emergency" differs from that of ambulatory hypertensive emergency/urgency because of the occurrence of this unique clinical situation in an atypical (postoperative) setting. Notably, moderately elevated BP values in the postoperative setting may require immediate treatment.[85]

Postoperative hypertensive emergency (POHE) is arbitrarily defined as elevation of SBP to levels > 190 mmHg and/or DBP to levels > 100 mmHg confirmed in two consecutive readings during the immediate postoperative period.[86] A 40 to 50 mmHg elevation in SBP or increase in BP values greater than 20% in relation to baseline values may also characterize postoperative hypertension.[87] This increase in BP values usually begins 10 to 20 minutes after surgery and can last up to 4 hours. The pathophysiology of POHE in patients previously normotensive is associated with peripheral vasoconstriction, catecholamine release, reduced baroreceptor sensitivity, central adrenergic activation, vasopressin release, stimulation of the renin-angiotensin system with consequent angiotensin II production, release of inflammatory cytokines (IL-6), and sodium retention. All these changes result in vasoconstriction, increase in afterload and SBP/DBP, and tachycardia. If left untreated, postoperative hypertension increases the risk of myocardial ischemia, AMI, APE, stroke, and bleeding, as well as postoperative mortality.[88,89]

POHE occurs in 40 to 80% of the patients undergoing carotid endarterectomy or open cardiac surgery, 57% of the patients undergoing abdominal aortic surgery and 29% of those undergoing peripheral vascular surgery.[90-92] In particular, acute and severe hypertension with SBP elevation > 220 mmHg may occur in 9% of the individuals undergoing carotid endarterectomy.[93] This manifestation, which may be transient, is related to carotid sinus manipulation and may cause hematoma, myocardial ischemia, and cerebral hyperperfusion with consequent neurological damage.[94] Other proposed mechanisms include iatrogenic denervation,[95] decreased baroreflex activity,[96] reduced carotid sinus sensitivity, and increased production of cerebral renin and/or catecholamines.[97,98]

HE may also occur after surgical correction of aortic coarctation. The etiology is multifactorial and includes changes in the baroreceptor reflex, activation of the sympathetic system and renin-angiotensin system, and expansion of the extracellular volume.[99] The stimulation of sympathetic nerve fibers located in the middle layer and adventitia of the aortic isthmus has two effects, both resulting in hypertension. Initially, peripheral release of norepinephrine occurs, with consequent vasoconstriction and BP elevation. Next, stimulation of juxtaglomerular cells occurs, releasing renin and promoting additional hypertension. Secondarily, increased renin production causes blood shunting from the mesenteric arteries, thus triggering abdominal symptoms in the so-called post-coarctectomy syndrome.[100]

Before initiating antihypertensive pharmacological treatment, reversible causes of postoperative hypertension should be investigated, such as pain, hypoxia, hypercapnia, agitation, bladder distension, and hypervolemia.[101] Proper analgesia and sedation are considered to be requirements before the initiation of antihypertensive therapy.[102] When POHE is present, the distinction between emergency and urgency is mandatory.[1-4] The therapeutic goal is not necessarily to normalize BP but to interrupt the vascular injury and reverse the pathological process. Progressive BP reductions, as reported in the general principles of HE treatment, should be achieved.[1]

References

1. Malachias MVB, Barbosa ECD, Martim JF, Rosito GBA, Toledo JY, Passarelli OJ. 7th Brazilian Guideline of Arterial Hypertension: Chapter 14 - Hypertensive Crisis. Arq Bras Cardiol. 2016;107(3 Suppl 3):79-83.
2. Martin JFV, Ribeiro JM. Urgências e Emergências Hipertensivas. In: Moreira MC, Montenegro ST, Paola AAV, eds. Livro Texto da Sociedade Brasileira de Cardiologia. 2 ed. Barueri (SP): Manole; 2015:p.922-30.
3. Elliott WJ. Clinical features in the management of selected hypertensive emergencies. Prog Cardiovasc Dis. 2006;48(5):316-325.
4. Ipek E, Oktay AA, Krim SR. Hypertensive crisis: an update on clinical approach and management. Curr Opin Cardiol. 2017;32(4):397-406.
5. Elliott WJ. Hypertensive Emergencies and Urgencies. In: Henry RB, William J, eds. Hypertension A Companion to Braunwald's Heart Disease. Philadelphia, PA: Elsevier (Saunders); 2013:390-394.
6. Heath I. Hypertensive Urgency-Is This a Useful Diagnosis? JAMA Intern Med. 2016;176(7):988-989.
7. Bortolotto LA, Silveira JV, Vilela-Martin JF. Hypertensive Crisis: Defining the Severity and Treatment. Revista da Sociedade de Cardiologia do Estado de São Paulo. 2018;28(3):254-259.
8. Suneja M, Sanders ML. Hypertensive Emergency. Med Clin North Am. 2017;101(3):465-478.
9. Janke AT, McNaughton CD, Brody AM, Welch RD, Levy PD. Trends in the Incidence of Hypertensive Emergencies in US Emergency Departments From 2006 to 2013. J Am Heart Assoc. 2016;5(12):pii e004511
10. Martin JF, Higashiama E, Garcia E, Luizon MR, Cipullo JP. Hypertensive crisis profile. Prevalence and clinical presentation. Arq Bras Cardiol. 2004;83(2):131-6;125-30.
11. Vilela-Martin JF, Vaz-de-Melo RO, Kuniyoshi CH, Abdo AN, Yugar-Toledo JC. Hypertensive crisis: clinical-epidemiological profile. Hypertens Res. 2011;34(3):367-371.
12. Pinna G, Pascale C, Fornengo P, et al. Hospital admissions for hypertensive crisis in the emergency departments: a large multicenter Italian study. PLoS One. 2014;9(4):e93542.
13. Taylor DA. Hypertensive Crisis: A Review of Pathophysiology and Treatment. Crit Care Nurs Clin North Am. 2015;27(4):439-447.
14. Varounis C, Katsi V, Nihoyannopoulos P, Lekakis J, Tousoulis D. Cardiovascular Hypertensive Crisis: Recent Evidence and Review of the Literature. Front Cardiovasc Med. 2016 Jan 10;3:51.
15. van den Born BJ, Lowenberg EC, van der Hoeven NV, et al. Endothelial dysfunction, platelet activation, thrombogenesis and fibrinolysis in patients with hypertensive crisis. J Hypertens. 2011;29(5):922-927.
16. Laragh J. Laragh's lessons in pathophysiology and clinical pearls for treating hypertension. Am J Hypertens. 2001;14(5 Pt 1):397-404.
17. Laragh JH. Vasoconstriction-volume analysis for understanding and treating hypertension: the use of renin and aldosterone profiles. Am J Med. 1973;55(3):261-274.
18. Blumenfeld JD, Laragh JH. Management of hypertensive crises: the scientific basis for treatment decisions. Am J Hypertens. 2001;14(11 Pt 1):1154-1167.
19. Strandgaard S, Olesen J, Skinhoj E, Lassen NA. Autoregulation of brain circulation in severe arterial hypertension. Br Med J. 1973;1(5852):507-510.
20. Bertel O, Marx BE, Conen D. Effects of antihypertensive treatment on cerebral perfusion. Am J Med. 1987;82(3B):29-36.
21. Andrade DO, Santos SPO, Pinhel MAS, et al. Effects of acute blood pressure elevation on biochemical-metabolic parameters in individuals with hypertensive crisis. Clin Exp Hypertens. 2017;39(6):553-561.
22. Vilela-Martin JF, Yugar-Toledo JC. Hypertensive Urgencies and Emergencies: Clinical Update. J J Emergen Med. 2014;2(1):007.
23. Kaplan NM, Victor RG. Hypertensive emergencies. Kaplan's Clinical Hypertensive. 11ed. Philadelphia, (PA): LWW;2015. p.263-74.
24. Elliott WJ. Clinical features and management of selected hypertensive emergencies. J Clin Hypertens (Greenwich). 2004;6(10):587-592.
25. Flanigan JS, Vitberg D. Hypertensive emergency and severe hypertension: what to treat, who to treat, and how to treat. Med Clin North Am. 2006;90(3):439-451.

Statement

26. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42(6):1206-1252.

27. Varon J. Treatment of acute severe hypertension: current and newer agents. Drugs. 2008;68(3):283-297.

28. van den Born BH, Lip GYH, Brguljan-Hitij J, et al. ESC Council on hypertension position document on the management of hypertensive emergencies. Eur Heart J Cardiovasc Pharmacother. 2019;5(1):37-46.

29. Phillips SJ, Whisnant JP. Hypertension and the brain. The National High Blood Pressure Education Program. Arch Intern Med. 1992;152(5):938-945.

30. Vaughan CJ, Delanty N. Hypertensive emergencies. Lancet. 2000;356(9227):411-417.

31. Schwartz RB, Mulkern RV, Gudbjartsson H, Jolesz F. Diffusion-weighted MR imaging in hypertensive encephalopathy: clues to pathogenesis. AJNR Am J Neuroradiol. 1998;19(5):859-862.

32. Ledingham JG, Rajagopalan B. Cerebral complications in the treatment of accelerated hypertension. Q J Med. 1979;48(189):25-41.

33. Haas DC, Streeten DH, Kim RC, Naalbandian AN, Obeid AI. Death from cerebral hypoperfusion during nitroprusside treatment of acute angiotensin-dependent hypertension. Am J Med. 1983;75(6):1071-1076.

34. Ahmed ME, Walker JM, Beevers DG, Beevers M. Lack of difference between malignant and accelerated hypertension. Br Med J (Clin Res Ed). 1986;292(6515):235-237.

35. Fahr T. Uner Nephrosklerose. Virchows Arch Pathol Anat. 1919;226(2):119-78.

36. Clough CG, Beevers DG, Beevers M. The survival of malignant hypertension in blacks, whites and Asians in Britain. J Hum Hypertens. 1990;4(2):94-6.

37. Lip GY, Beevers M, Beevers DG. Complications and survival of 315 patients with malignant-phase hypertension. J Hypertens. 1995;13(8):915-24.

38. Lane DA, Lip GY, Beevers DG. Improving survival of malignant hypertension patients over 40 years. Am J Hypertens. 2009;22(11):1199-204.

39. Silva HB, Bortolotto LA, Giorgi DM, Frimm CC, Giorgi Mc, Bellotti G, et al. Ventricular function by radionuclide ventriculography in malignant hypertension. Hypertension. 1992;19(2 Suppl):II210-II213.

40. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2018;49(3):e46-e110.

41. Anderson CS, Heeley E, Huang Y, Wang j, Delcourt C, Lindley R, et al.et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med. 2013;368(25):2355-2365.

42. Qureshi AI, Palesch YY, Barsan WG,Hanley DF, Hsu CY, Martin RL, et al. Intensive Blood-Pressure Lowering in Patients with Acute Cerebral Hemorrhage. N Engl J Med. 2016;375(11):1033-43.

43. Royal College of Physicians. National clinical guideline for stroke. 2016:1-148.

44. Williams B, Mancia G, Spiering W, Agabiti Rosei, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39(33):3021-104.

45. Herlitz J, Karlson BW, Lindqvist J, Sjolin M. Prognosis during five years of follow-up among patients admitted to the emergency department with acute chest pain in relation to a history of hypertension. Blood Press. 1998;7(2):81-8.

46. Pattanshetty DJ, Bhat PK, Aneja A, Pillai DP. Elevated troponin predicts long-term adverse cardiovascular outcomes in hypertensive crisis: a retrospective study. J Hypertens. 2012;30(12):2410-5.

47. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-Elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. J Am Coll Cardiol. 2007;50(7):e1-e157.

48. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, Lemos JA, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;61(4):485-510.

49. Wright RS, Anderson JL, Adams CD,Bridges CR, Casey DE Jr, Ettinger SM, et al. 2011 ACCF/AHA focused update incorporated into the ACC/AHA 2007 Guidelines for the Management of Patients with Unstable Angina/Non-ST-Elevation Myocardial Infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines developed in collaboration with the American Academy of Family Physicians, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. J Am Coll Cardiol. 2011;57(19):e215-367.

50. Rodriguez MA, Kumar SK, De Caro M. Hypertensive crisis. Cardiol Rev. 2010;18(2):102-7.

51. Keating GM. Clevidipine: a review of its use for managing blood pressure in perioperative and intensive care settings. Drugs. 2014;74(16):1947-60.

52. Papadopoulos DP, Mourouzis I, Thomopoulos C, Makris T, Papademetriou V. Hypertension crisis. Blood Press. 2010;19(6):328-36.

53. Bangalore S, Messerli FH, Kostis JB, Pepine CJ. Cardiovascular protection using beta-blockers: a critical review of the evidence. J Am Coll Cardiol. 2007;50(7):563-72.

54. Messerli FH, Panjrath GS. The J-curve between blood pressure and coronary artery disease or essential hypertension: exactly how essential? J Am Coll Cardiol. 2009;54(20):1827-34.

55. Bangalore S, Qin J, Sloan S, Murphy SA, Cannon CP. What is the optimal blood pressure in patients after acute coronary syndromes?: Relationship of blood pressure and cardiovascular events in the PRavastatin OR atorVastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction (PROVE IT-TIMI) 22 trial. Circulation. 2010;122(21):2142-51.

56. Gandhi SK, Powers JC, Nomeir AM,Fowle K, Kitza DW, Rankin KM, et al. The pathogenesis of acute pulmonary edema associated with hypertension. N Engl J Med. 2001;344(1):17-22.

57. Kumar R, Gandhi SK, Little WC. Acute heart failure with preserved systolic function. Crit Care Med. 2008;36(1 Suppl):S52-56.

58. Peacock WF, Braunwald E, Abraham W,Albert N, Burnett J, Christenson R, et al. National Heart, Lung, and Blood Institute working group on emergency department management of acute heart failure: research challenges and opportunities. J Am Coll Cardiol. 2010;56(5):343-51.

59. Comitê Coordenador da Diretriz de Insuficiência Cardíaca da Sociedade Brasileira de Cardiologia; Rohde LEP, Montera MW, Bocchi EA, Albuquerque DC, Clausell NO, Rassi S, et al.et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol. 2018;111(3):436-539.

60. Morris JH, Mix D, Cameron SJ. Acute Aortic Syndromes: Update in Current Medical Management. Curr Treat Options Cardiovasc Med. 2017;19(4):29.

61. Mussa FF, Horton JD, Moridzadeh R, Nicholson J, Trimarchi S, Eagle KA. Acute Aortic Dissection and Intramural Hematoma: A Systematic Review. JAMA. 2016;316(7):754-63.

62. Andersen ND, Ganapathi AM, Hanna JM, Williams JB, Gaca JG, Hughes GC. Outcomes of acute type a dissection repair before and after implementation of a multidisciplinary thoracic aortic surgery program. J Am Coll Cardiol. 2014;63(17):1796-803.

63. Nienaber CA, Powell JT. Management of acute aortic syndromes. Eur Heart J. 2012;33(1):26-35b.

64. Erbel R, Aboyans V, Boileau C, Bossone E, Bartolomeu RD, Eggerecht H, et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases: Document covering acute and chronic aortic diseases of the thoracic and abdominal aorta of the adult. The Task Force for the Diagnosis and Treatment of Aortic Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2014;35(41):2873-926.

65. Hiratzka LF, Bakris GL, Beckman JA, Bersin RM, Carr VF, Casey DE Jr, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the diagnosis and management of patients with thoracic aortic disease. A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology,American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons,and Society for Vascular Medicine. J Am Coll Cardiol. 2010;55(14):e27-e129.

66. Fattori R, Tsai TT, Myrmel T, Evangelista A, Cooper CV, Trimarchi S, et al. Complicated acute type B dissection: is surgery still the best option?: a report from the International Registry of Acute Aortic Dissection. JACC Cardiovasc Interv. 2008;1(4):395-402.

67. Suzuki T, Isselbacher EM, Nienaber CA, Ryeritz RE, eagle KA, Tsai T, et al. Type-selective benefits of medications in treatment of acute aortic dissection (from the International Registry of Acute Aortic Dissection [IRAD]). Am J Cardiol. 2012;109(1):122-7.

68. Takeshita S, Sakamoto S, Kitada S, Akutsu K, Hashimoto H. Angiotensin-converting enzyme inhibitors reduce long-term aortic events in patients with acute type B aortic dissection. Circ J. 2008;72(11):1758-61.

69. Wemmelund H, Hogh A, Hundborg HH, Thomsen RW, Johnsen SP, Lindholt JS. Statin use and rupture of abdominal aortic aneurysm. Br J Surg. 2014;101(8):966-75.

70. Alexander JM, Wilson KL. Hypertensive emergencies of pregnancy. Obstet Gynecol Clin North Am. 2013;40(1):89-101.

71. Deak TM, Moskovitz JB. Hypertension and pregnancy. Emerg Med Clin North Am. 2012;30(4):903-17.

72. Malachias MV, Figueiredo CE, Sass N, Antonello IC, Torloni MR, Bortolotto ML. 7th Brazilian Guideline of Arterial Hypertension: Chapter 9 - Arterial Hypertension in pregnancy. Arq Bras Cardiol. 2016;107(3 Suppl 3):49-52.

73. Sibai BM, Grossman RA, Grossman HG. Effects of diuretics on plasma volume in pregnancies with long-term hypertension. Am J Obstet Gynecol. 1984;150(7):831-5.

74. Ramachandran R, Rewari V. Current perioperative management of pheochromocytomas. Indian J Urol. 2017;33(1):19-25.

75. Malachias MVB, Bortolotto LA, Drager LF, Borelli FAO, Lotaif LAD, Martins LC. 7th Brazilian Guideline of Arterial Hypertension: Chapter 12 - Secondary Arterial Hypertension. Arq Bras Cardiol. 2016;107(3 Suppl 3):67-74.

76. Lenders JW, Duh QY, Eisenhofer G, Gimenez-Roqueplo AP, Grebe SK, Murad MH, et al. Pheochromocytoma and paraganglioma: an endocrine society clinical practice guideline. J Clin Endocrinol Metab. 2014;99(6):1915-42.

77. Plouin PF, Amar L, Dekkers OM,Fassnacht M, Gimenez-Roqueplo AP, Lenders JW, et al. European Society of Endocrinology Clinical Practice Guideline for long-term follow-up of patients operated on for a phaeochromocytoma or a paraganglioma. Eur J Endocrinol. 2016;174(5):G1-G10.

78. Muscholl E. Effect of cocaine and related drugs on the uptake of noradrenaline by heart and spleen. Br J Pharmacol Chemother. 1961;16:352-9.

79. Foltin RW, Ward AS, Haney M, Hart CL, Collins ED. The effects of escalating doses of smoked cocaine in humans. Drug Alcohol Depend. 2003;70(2):149-57.

80. Foltin RW, Fischman MW. Ethanol and cocaine interactions in humans: cardiovascular consequences. Pharmacol Biochem Behav. 1988;31(4):877-83.

81. Wilbert-Lampen U, Seliger C, Zilker T, Arendt RM. Cocaine increases the endothelial release of immunoreactive endothelin and its concentrations in human plasma and urine: reversal by coincubation with sigma-receptor antagonists. Circulation. 1998;98(5):385-90.

82. Mo W, Singh AK, Arruda JA, Dunea G. Role of nitric oxide in cocaine-induced acute hypertension. Am J Hypertens. 1998;11(6 Pt 1):708-14.

83. Brogan WC, 3rd, Lange RA, Kim AS, Moliterno DJ, Hillis LD. Alleviation of cocaine-induced coronary vasoconstriction by nitroglycerin. J Am Coll Cardiol. 1991;18(2):581-6.

84. Lange RA, Cigarroa RG, Flores ED, McBride W, Kim AS, Wells PJ, et al. Potentiation of cocaine-induced coronary vasoconstriction by beta-adrenergic blockade. Ann Intern Med. 1990;112(12):897-903.

85. Aronson S. Perioperative hypertensive emergencies. Curr Hypertens Rep. 2014;16(7):448.

86. Varon J, Marik PE. Perioperative hypertension management. Vasc Health Risk Manag. 2008;4(3):615-27.

87. Goldberg ME, Larijani GE. Perioperative Hypertension. Pharmacotherapy: J Human Pharmacol Drug Ther.1998;18(5):911-4.

88. Rose DK, Cohen MM, DeBoer DP. Cardiovascular events in the postanesthesia care unit: contribution of risk factors. Anesthesiology. 1996;84(4):772-81.

89. Marik PE, Varon J. Perioperative hypertension: a review of current and emerging therapeutic agents. J Clin Anesth. 2009;21(3):220-9.

90. Goldman L, Caldera DL. Risks of general anesthesia and elective operation in the hypertensive patient. Anesthesiology. 1979;50(4):285-92.

91. Leslie JB. Incidence and aetiology of perioperative hypertension. Acta Anaesthesiol Scand Suppl. 1993;99:5-9.

92. Lien SF, Bisognano JD. Perioperative Hypertension: Defining At-Risk Patients and Their Management. Curr Hypertens Rep. 2012;14(5):432-41.

93. Wong JH, Findlay JM, Suarez-Almazor ME. Hemodynamic instability after carotid endarterectomy: risk factors and associations with operative complications. Neurosurgery. 1997;41(1):35-41; discussion 41-33.

94. Stoneham MD, Thompson JP. Arterial pressure management and carotid endarterectomy. BJA. 2009;102(4):442-52.

95. Sigaudo-Roussel D, Evans DH, Naylor AR, Panerai R. Deterioration in carotid baroreflex during carotid endarterectomy. J Vasc Surg. 2002;36(4):793-8.

96. Nouraei SA, Al-Rawi PG, Sigaudo-Roussel D, Giussani DA, Gaunt ME. Carotid endarterectomy impairs blood pressure homeostasis by reducing the physiologic baroreflex reserve. J Vasc Surg. 2005;41(4):631-7.

97. Smith BL. Hypertension following carotid endarterectomy: the role of cerebral renin production. J Vasc Surg. 1984;1(5):623-7.

98. Hans SS, Prakash S, Hans P, Glover JL. The role of renin and catecholamine production in postcarotid endarterectomy hypertension. Surg Gynecol Obstet. 1992;174(3):201-4.

99. Sealy WC. Paradoxical hypertension after repair of coarctation of the aorta: a review of its causes. Ann Thorac Surg. 1990;50(2):323-9.

100. Fox S, Pierce WS, Waldhausen JA. Pathogenesis of paradoxical hypertension after coarctation repair. Ann Thorac Surg. 1980;29(2):135-41.

101. Samson RH. Periprocedural hypertension: current concepts in management for the vascular surgeon. Vasc Endovascular Surg. 2004;38(4):361-6.

102. Haas CE, LeBlanc JM. Acute postoperative hypertension: a review of therapeutic options. Am J Health Syst Pharm. 2004;61(16):1661-73; quiz 1674-5.

This is an open-access article distributed under the terms of the Creative Commons Attribution License