ABC Cardiol
Arquivos Brasileiros de Cardiologia

Volume 117 | Number 2
August 2020

Brazilian Society of Cardiology
ISSN-0066-782X

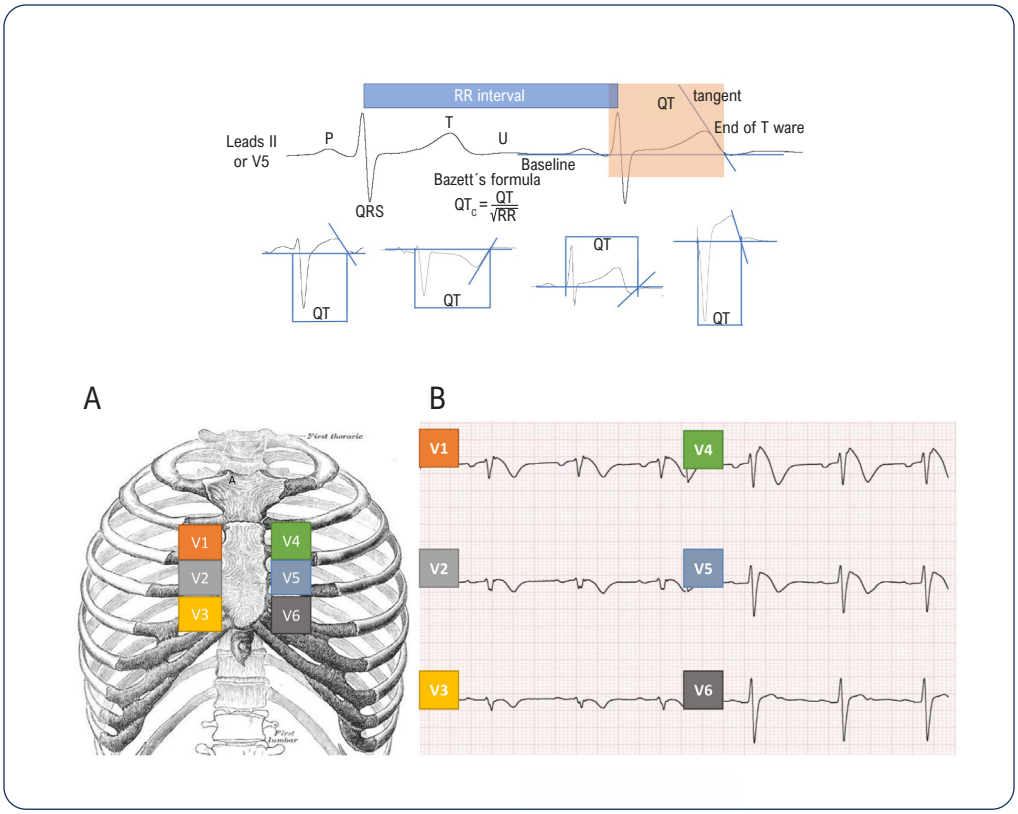


Figure 1 and 2, pages 396 and 397.

Statin Use Improves Cardiometabolic Protection Promoted By Physical Training in an Aquatic Environment: A Randomized Clinical Trial

Association between Clinical Risk Score (Heart, Grace and TIMI) and Angiographic Complexity in Acute Coronary Syndrome without ST Segment Elevation

Naringin and Trimetazidine Improve Baroreflex Sensitivity and Nucleus Tractus Solitarius Electrical Activity in Renal Ischemia-Reperfusion Injury

Characteristics and Temporal Trends in the Mortality of Different Heart Failure Phenotypes in Primary Care

Physiological Responses to Maximal and Submaximal Walking in Patients with Symptomatic Peripheral Artery Disease

In- and Out-of-Hospital Deaths by Acute Myocardial Infarction in Brazilian State Capitals

Cardiovascular and Cancer Death Rates in the Brazilian Population Aged 35 to 74 Years, 1996-2017

Prevalence and Related Characteristics of Patients with Brugada Pattern Electrocardiogram in Santa Catarina, Brazil

Peculiar Aspects of Patients with Inherited Arrhythmias during the COVID-19 Pandemic

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

Contents

Editorial

Impact Factor of 2.0, a New Historical Record for ABC Cardiol – Many Thanks to our Cardiology and Scientific Community

Carlos Eduardo Rochitte

.....page 266

Original Article

Statin Use Improves Cardiometabolic Protection Promoted By Physical Training in an Aquatic Environment: A Randomized Clinical Trial

Rochelle Rocha Costa, Alexandra Ferreira Vieira,Leandro Coconcelli,Alex de Oliveira Fagundes,Adriana Cristine Koch Buttelli,Laura Frances Pereira, Ricardo Stein, Luiz Fernando Martins Kruel

.....page 270

Short Editorial

Statin Associated With Physical Training: A Perfect Combination

Stephanie Bastos da Motta, Vanessa Caroline Toledes, Leandro Franzoni

.....page 279

Original Article

Association between Clinical Risk Score (Heart, Grace and TIMI) and Angiographic Complexity in Acute Coronary Syndrome without ST Segment Elevation

Alexandre Vianna Cedro, Diandro Marinho Mota, Louis Nakayama Ohe, Ari Timerman, José Ribamar Costa, Laura de Siqueira Castro

.....page 281

Short Editorial

NSTE-ACS at the Emergency: Can You Guess What is Under the Umbrella?

Bruno Rocha and Carlos Aguiar

.....page 288

Original Article

Naringin and Trimetazidine Improve Baroreflex Sensitivity and Nucleus Tractus Solitarius Electrical Activity in Renal Ischemia-Reperfusion Injury

Negin Amini, Alireza Sarkaki, Mahin Dianat, Seyyed Ali Mard, Akram Ahangarpour, Mohammad Badavi

.....page 290

Short Editorial

Naringin, Trimetazidine and Baroreflex in Renal Ischemia-Reperfusion Injury
Luis Cuadrado Martin
.....page 298

Original Article

Characteristics and Temporal Trends in the Mortality of Different Heart Failure Phenotypes in Primary Care
Antonio José Lagoeiro Jorge, Leticia Mara dos Santos Barbetta, Eduardo Thadeu de Oliveira Correia, Wolney de Andrade Martins, Adson Renato Leite, Maria Auxiliadora Nogueira Saad, Márcia Maria Sales dos Santos, Dayse Mary Correia, Maria Luiza Garcia Rosa, Sérgio Chermont, Cárita Cunha dos Santos, Evandro Tinoco Mesquita
.....page 300

Short Editorial

Heart Failure with Mid-Range Ejection Fraction – A Temporary Condition or a Specific Group?
Eduardo Arrais Rocha, Camila Pinto Cavalcante Miná, Maria Eduarda Quidute Arrais Rocha
.....page 307

Original Article

Physiological Responses to Maximal and Submaximal Walking in Patients with Symptomatic Peripheral Artery Disease
Marcel Chehuen, Aluisio Andrade-Lima, Natan Silva Junior, Roberto Miyasato, Rodrigo W. Alves de Souza, Anthony Leicht, Patricia Chakur Brum, Edilamar M. Oliveira, Nelson Wolosker, Claudia Lucia de Moraes Forjaz
.....page 309

Short Editorial

The Paradox of Exercise Intensity in Preventing Cardiovascular Events in Peripheral Arterial Occlusive Disease
Pablo de Souza and Cássio Perfete
.....page 317

Original Article

In- and Out-of-Hospital Deaths by Acute Myocardial Infarction in Brazilian State Capitals
Sterffeson Lamare Lucena de Abreu, Joana D'Arc Matos França de Abreu, Maria dos Remédios Freitas Carvalho Branco, Alcione Miranda dos Santos
.....page 319

Short Editorial

Acute Myocardial Infarction Death Rates in Brazil - A Small Light at the End of the Tunnel
Ana Teresa Timóteo
.....page 327

Original Article

Cardiovascular and Cancer Death Rates in the Brazilian Population Aged 35 to 74 Years, 1996-2017
Antonio de Padua Mansur and Desiderio Favarato
.....page 329

Short Editorial

Successes and Challenges in the Management of Cardiovascular Disease in Brazil: Living Longer and Better

Bruno Fernandes Galdino, David Costa Peixoto, Ana Carolina Alves, Bruno Ramos Nascimento, Luisa Campos Caldeira Brant

.....page 341

Original Article

Prevalence and Related Characteristics of Patients with Brugada Pattern Electrocardiogram in Santa Catarina, Brazil

Mariana Sarmento Militz, Andrei de Souza Inacio, Harley Miguel Wagner, Aldo von Wangenheim, Alexander Romeno Janner Dal Forno, Daniel Medeiros Moreira

.....page 343

Short Editorial

Brugada ECG Pattern – A Blip on the Radar for a Potentially Life-Threatening Condition

Mirella Facin

.....page 350

Original Article

Breaks in Sedentary Time and Cardiometabolic Markers in Adolescents

Natália Maria Mesquita de Lima Quirino, Alcides Prazeres Filho, Arthur Oliveira Barbosa, Gerfeson Mendonça, José Cazuza de Farias Júnior

.....page 352

Short Editorial

Is Adolescents' Cardiometabolic Health Affected by Prolonged Periods of Inactivity?

Andrea Wendt

.....page 363

Original Article

The Effect of Atorvastatin + Aspirin on the Endothelial Function Differs with Age in Patients with HIV: A Case-Control Study

Gerson Gomes dos Santos Junior, Paulo Sérgio Ramos Araújo,Kaliene Maria Estevão Leite, Emmanuelle Tenório Godoi, Adriana Ferraz Vasconcelos, Heloisa Ramos Lacerda

.....page 365

Short Editorial

For which HIV Patients Aspirin and Statins are Good?

Théo Pezel, Layde R. Paim, Otávio R. Coelho-Filho

.....page 376

Original Article

Arterial Hypertension and Serum Uric Acid in Elderly- SEPHAR III Study

Roxana Buzas, Vlad-Sabin Ivan, Oana-Florentina Gheorghe-Fronea, Adina Flavia Morgovan, Melania Ardelean, Nicolae Albulescu, Maria Dorobantu, Daniel Florin Lighezan

.....page 378

Original Article

Type 1 Cardiorenal Syndrome in Decompensated Heart Failure Patients in a Low-Income Region in Brazil: Incidence of Acute Kidney Injury (AKIN and KDIGO Criteria), Need for Dialysis and Mortality

Ginivaldo Victor Ribeiro do Nascimento, Heitor Carlos Domingues de Brito, Carlos Eduardo Batista de Lima ..... page 385

Short Editorial

Assessment of Renal Function in Patients with Heart Failure

Alfredo Jose Mansur and Victor Sarli Issa ..... page 392

Review Article

Peculiar Aspects of Patients with Inherited Arrhythmias during the COVID-19 Pandemic

Luciana Sacilotto, Natalia Quintella Sangiorgi Olivetti, Cristiano Faria Pisani, Tan Chen Wu, Ludhmila Abrahão Hajjar, Sissy Lara de Melo, Sávia Christina Pereira Bueno, Esteban Wisnivesky Rocca Rivarola, Muhieddine Omar Chokr, Carina Abigail Hardy, Denise Tessariol Hachul, Francisco Carlos da Costa Darrieux, Mauricio Ibrahim Scanavacca ..... page 394

Research Letter

Patient in Cardiorespiratory Arrest - Is it Possible to Perform Transcatheter Aortic Valve Implantation (TAVI) in this Scenario?

Alexandre de Matos Soeiro, Francisco Akira Cardozo, Patrícia Oliveira Guimarães, Marcel Paula Pereira, Paulo Vinícius Ramos Souza, Gustavo A. B. Boros, Viviane Cordeiro Veiga, Samolon Soriano Ordinola Rojas, Fernanda Marinho Mangione, Salvador André Bavaresco Cristóvão, Gustavo Alexandre Dutra, Adnan Ali Salman, Luiz Eduardo Loureiro Bettarello, José Armando Mangione ..... page 404

Research Letter

Unusual Finding of Rare Exuberant Xanthomatosis in Hyperlipidemia

Enrico Manfredini and Renato Jorge Alves ..... page 407

Research Letter

SARS-CoV-2 and Myocardical Injury with ST-Elevation without Coronary Disease

Carolina Ragonetti, Enzo Oku Martinazzo, Felipe Montesano Fazionato, Guilherme Osório Guimarães Ferreira, Milena Piccolo Santana, Camila Hartmann ..... page 411

Letter to the Editor

Cardiovascular Imaging in COVID-19

Rujittika Mungmungpuntitpantip e Viroj Wiwanitkit ..... page 415

Brief Communication

Prevalence of Systemic Arterial Hypertension and Diabetes Mellitus in Individuals with COVID-19: A Retrospective Study of Deaths in Pernambuco, Brazil

Lucas Gomes Santos, Jussara Almeida de Oliveira Baggio, Thiago Cavalcanti Leal, Francisco A. Costa, Tânia Rita Moreno de Oliveira Fernandes, Regicley Vieira da Silva, Anderson Armstrong, Rodrigo Feliciano Carmo, Carlos Dornels Freire de Souza ..... page 416

Erratum

..... page 423

ABC Cardiol

Arquivos Brasileiros de Cardiologia

JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

Sociedade Brasileira de Cardiologia

President (Leave of absence)
Marcelo Antônio Cartaxo Queiroga Lopes

President
Celso Amodeo

Financial Director
Ricardo Mourilhe Rocha

Scientific Director
Fernando Bacal

Managing Director
Olga Ferreira de Souza

Service Quality Director
Sílvio Henrique Barberato

Communication Director
Harry Corrêa Filho

Information Technology Director
Leandro Ioschpe Zimerman

Governmental Relations Director
Nasser Sarkis Simão

State and Regional Relations Director
João David de Souza Neto

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

Director of Specialized Departments
Andréa Araujo Brandão

Research Director
David de Pádua Brasil

Coordinator of Science, Technology and Innovation
Ludhmila Abrahão Hajjar

Coordinator of Continued Medical Education
Brivaldo Markman Filho

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

Coordinator of Compliance and Transparency
Marcelo Matos Cascudo

Coordinator of Strategic Affairs
Hélio Roque Figueira

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

Editor-in-Chief of the IJCS
Claudio Tinoco Mesquita

Coordinator of the University of the Heart
Evandro Tinoco Mesquita

Coordinator of Standards and Guidelines
Brivaldo Markman Filho

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

SBC/AM – Kátia do Nascimento Couceiro

SBC/BA – Gilson Soares Feitosa Filho

SBC/CE – Gentil Barreira de Aguiar Filho

SBC/DF – Alexandra Oliveira de Mesquita

SBC/ES – Tatiane Mascarenhas Santiago Emerich

SBC/GO – Leonardo Sara da Silva

SBC/MA – Mauro José Mello Fonseca

SBC/MG – Henrique Patrus Mundim Pena

SBC/MS – Gabriel Doreto Rodrigues

SBC/MT – Marcos de Thadeu Tenuta Junior

SBC/NNE – Nivaldo Menezes Filgueiras Filho

SBC/PA – Dilma do Socorro Moraes de Souza

SBC/PB – Lenine Angelo Alves Silva

SBC/PE – Fernando Ribeiro de Moraes Neto

SBC/PI – Luiz Bezerra Neto

SBC/PR – Raul DAurea Mora Junior

SOCERJ – Wolney de Andrade Martins

SBC/RN – Maria Sanali Moura de Oliveira Paiva

SOCERON – Daniel Ferreira Mugrabi

SOCERGS – Mario Wiehe

SBC/SC – Amberson Vieira de Assis

SBC/SE – Eryca Vanessa Santos de Jesus

SOCESP – João Fernando Monteiro Ferreira

Presidents of the Specialized Departaments and Study Groups

SBC/DA – Antonio Carlos Palandri Chagas

SBC/DCC – Bruno Caramelli

SBC/DCC/CP – Klebia Magalhães Pereira Castello Branco

SBC/DCM – Celi Marques Santos

SBC/DECAGE – Izo Helber

SBC/DEIC – Evandro Tinoco Mesquita

SBC/DERC – Gabriel Leo Blacher Grossman

SBC/DFCVR – Antoinette Oliveira Blackman

SBC/DHA – Audes Diógenes de Magalhães Feitosa

SBC/DIC – Carlos Eduardo Rochitte

SBCCV – Eduardo Augusto Victor Rocha

SOBRAC – Ricardo Alkmim Teixeira

SBHCI – Ricardo Alves da Costa

DCC/GAPO – Danielle Menosi Gualandro

DCC/GECETI – Luiz Bezerra Neto

DCC/GECO – Roberto Kalil Filho

DCC/GEMCA – Roberto Esporcatte

DCC/GERTC – Adriano Camargo de Castro Carneiro

DEIC/GEICPED – Estela Azeka

DEIC/GEMIC – Marcus Vinicius Simões

DERC/GECESP – Clea Simone Sabino de Souza Colombo

DERC/GECN – Lara Cristiane Terra Ferreira Carreira

DERC/GERCPM – Carlos Alberto Cordeiro Hossri

GECIP – Marcelo Luiz da Silva Bandeira

GEECG – Carlos Alberto Pastore

DCC/GETA – Carlos Vicente Serrano Junior

DCC/GECRA – Sandra Marques e Silva

Arquivos Brasileiros de Cardiologia

Volume 117, Nº 2, August 2021

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

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

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

Editorial Production
SBC - Internal Publication Department

Graphic Design and Diagramming
SBC - Internal Design Department

Impact Factor of 2.0, a New Historical Record for ABC Cardiol – Many Thanks to our Cardiology and Scientific Community

Carlos Eduardo Rochitte[1,2]

Universidade de São Paulo, Faculdade de Medicina, Hospital das Clínicas - Instituto do Coração,[1] *São Paulo, SP - Brazil*
Hospital do Coração (HCOR), São Paulo[2] *SP – Brazil*

The Brazilian Society of Cardiology's most traditional scientific journal, with 73 years of history, *Arquivos Brasileiros de Cardiologia* or *ABC Cardiol*, has recently reached a new level of international recognition based on its 2020 impact factor, which is a new historical record.

ABC Cardiol's new impact factor is 2.0, as published by the 2020 Journal of Citation Report (JCR, Clarivate), which means that, on average, each article published in *ABC Cardiol* was cited 2 times by other articles. This represents the impact of scientific data published in *ABC Cardiol* in the actively productive scientific community. This index has been progressively rising over the past years, and the impact factor of 2 is not merely an isolated number (Figure 1).[1-4] It is also highly noteworthy that *ABC Cardiol* holds first place among cardiovascular science journals in Latin America in international rankings, such as Scopus (Figure 2).

This achievement was made possible by the credibility that *ABC Cardiol* has built in our scientific cardiology community in Brazil and worldwide. In fact, this result was achieved thanks to all the authors, reviewers, and editors who have continually supported the Brazilian Society of Cardiology's scientific journals. To all those who have supported us, I would like to say, "Thank you very much!"

I would also like to thank the Brazilian Society of Cardiology, represented by the recent Presidents who have been the driving forces on this journey, Dr. Oscar Dutra, Dr. Marcelo Queiroga, and Dr. Celso Amodeo. Once again, "Thank you very much!"

Also part of the Brazilian Society of Cardiology, our team of editorial assistants (Figure 3) is the true soul of our journal, and we would all like to send a big, "Thank you very much!"

The most important mission of this editorial is to say, "Thank you very much" to all those who are directly or indirectly involved in this wonderful result, which belongs to everyone who is part of our big cardiology community.

To cite a few data related to this new impact factor, the 274 articles published in *ABC Cardiol* in 2018 and 2019 were cited 548 times by other scientific articles. Many highly prestigious international journals have cited articles published in *ABC Cardiol*, including *Circulation*, *Journal of the American Heart Association*, *Journal of the American College of Cardiology*, *Atherosclerosis*, *Journal of Clinical Hypertension*, *International Journal of Molecular Sciences*, and many others. The cited articles include many original Brazilian and international articles. This year's impact factor relied less on citations of Brazilian Society of Cardiology Guidelines than that of previous years. Multiple Brazilian and international articles were cited a significant number of times in the international literature.

The contributions of postgraduate programs and Brazilian universities have been fundamental to our impact factor, and, once more, I would like to say, "Thank you very much!" The Brazilian institutions that contributed the most papers to *ABC Cardiol* during the past 3 years all have long-standing traditions in Brazilian Cardiology, and they are displayed in Figure 4.

Finally, the evolving quality of *ABC Cardiol* will make it possible to expand the scope of the Brazilian Society of Cardiology's scientific publications with the creation of a family of scientific journals.[5-6] Recently, the Brazilian Society of Cardiology released its newest scientific journal, *ABC Heart Failure & Cardiomyopathy*, which, in conjunction with the *International Journal of Cardiovascular Sciences* and *ABC Cardiovascular Imaging*, will compose the Brazilian Society of Cardiology's initial family of publications.

ABC Cardiol and the Brazilian Society of Cardiology's scientific journals have a bright and exciting future ahead of them. The Brazilian Society of Cardiology's scientific journals, on account of their credibility and responsibility,[7] constitute a high quality scientific vehicle at the service of Cardiology and the worldwide scientific community, right here in Brazil.

Keywords

Impact Factor; Scientific Publication Indicators; Journal Impact Factor; Cardiology.

Mailing Address: Carlos E. Rochitte •
Av. Dr. Enéas de Carvalho Aguiar 44 - Andar AB, Ressonância & Tomografia.
Postal Code: 05403-000, Cerqueira César, São Paulo, SP – Brazil.
E-mail: rochitte@cardiol.br

DOI: https://doi.org/10.36660/abc.20210616

Editorial

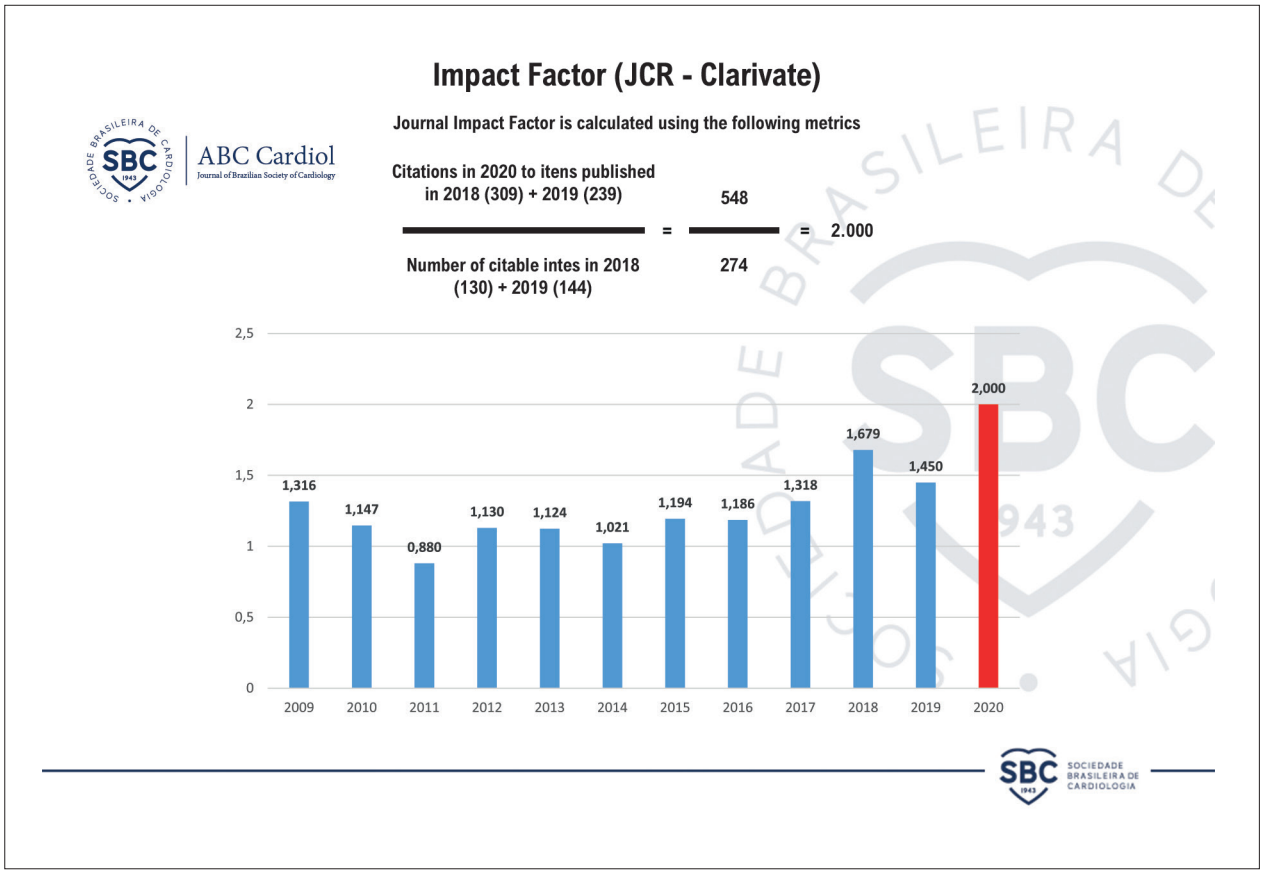


Figure 1 – Impact factor (JCR – Clarivate)

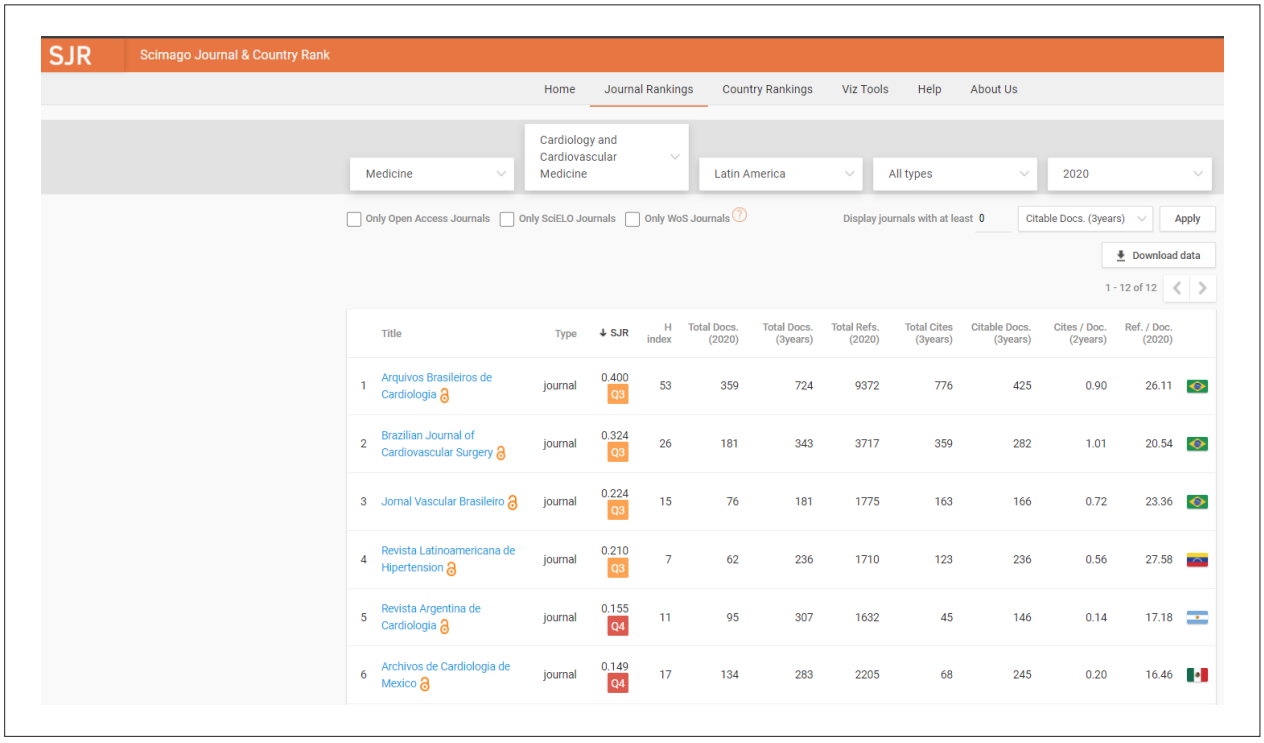


Figure 2 – *Ranking (SJR – Scimago).*

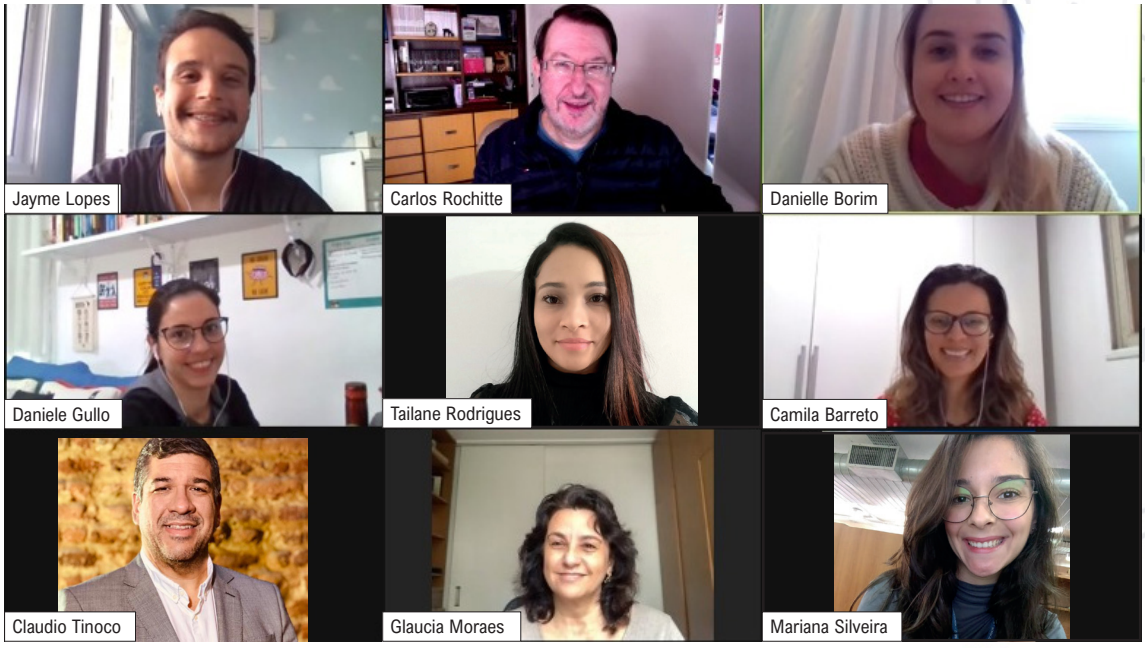


Figure 3 – *Editorial team in action.*

Organizations that have contributed the most papers to the journal in the most recent three-year period.

RANK	ORGANIZATION	COUNT
1	UNIVERSIDADE DE SAO PAULO	227
2	UNIVERSIDADE FEDERAL DO RIO DE JANEIRO	58
3	UNIVERSIDADE FEDERAL DE SAO PAULO (UNIFESP)	56
4	UNIVERSIDADE FEDERAL FLUMINENSE	49
5	INSTITUTO DANTE PAZZANESE DE CARDIOLOGIA	46
-	UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL	46
7	HOSPITAL ISRAELITA ALBERT EINSTEIN	42
-	UNIVERSIDADE FEDERAL DE MINAS GERAIS	42
9	UNIVERSIDADE ESTADUAL PAULISTA	41
10	HOSPITAL DO CORACAO - HCOR	36

Figure 4 – *Contributions of scientific institutions.*

References

1. Rochitte CE. The New Impact Factor of the Arquivos Brasileiros de Cardiologia (ABC Cardiol), 1.318: An Achievement of the SBC for Our Scientific Community.Arq Bras Cardiol. 2018 Jul;11(1):1-3 doi:10.5935/abc.20180129.
2. Rochitte CE. Just-Released JCR Impact Factor Shows Strong and Steady Increase for ABC Cardiol - 1.679 - A New Historical Record. Arq Bras Cardiol. 2019 Aug 8;113(1):1-4. doi: 10.5935/abc.20190135.
3. Rochitte CE, Quadros AS, Sousa AGMR, Ladeia AMT, Brandão AA, Lorenzo A, et al.Arquivos Brasileiros de Cardiologia (ABC Cardiol) and the new classification Qualis of Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES). Arq Bras Cardiol. 2019 Oct 10;113(3):333-4. doi:10.5935/abc.20190206.
4. Rochittre CE. ABC Cardiol - Our Home of the Cardiovascular Scientific Research. Arq Bras Cardiol. 2020 Dec;115(6):1044-6. doi: 10.36660/abc.20201206.
5. Rochitte CE. Interaction among Cardiovascular Scientific Journals in Brazil: A Model that should be Better Explored. Arq Bras Cardiol. 2020 Mar;114(3):433-4. doi: 10.36660/abc.20200159.
6. Evora PRB. The "Great Family" of Cardiovascular Scientific Journals in Brazil. Evora PRB. Braz J Cardiovasc Surg. 2020 Aug 1;35(4):I-II. doi: 10.21470/1678-9741-1-2020-0608.
7. Authorship: from credit to accountability. Reflections from the Editors' Network. Alfonso F, Zelveian P, Monsuez JJ, Aschermann M, Böhm M, Hernandez AB, Wang TD, Cohen A, Izetbegovic S, Doubell A, Echeverri D, Enç N, Ferreira-González I, Undas A, Fortmüller U, Gatzov P, Ginghina C, Goncalves L, Addad F, Hassanein M, Heusch G, Huber K, Hatala R, Ivanusa M, Lau CP, Marinskis G, Cas LD, Rochitte CE, Nikus K, Fleck E, Pierard L, Obradović S, Del Pilar Aguilar Passano M, Jang Y, Rødevand O, Sander M, Shlyakhto E, Erol Ç, Tousoulis D, Ural D, Piek JJ, Varga A, Flammer AJ, Mach F, Dibra A, Guliyev F, Mrochek A, Rogava M, Guzman Melgar I, Di Pasquale G, Kabdrakhmanov K, Haddour L, Fras Z, Held C, Shumakov V; Editors' Network, European Society of Cardiology (ESC) Task Force. Review. Basic Res Cardiol. 2019 Apr 8;114(3):23. doi: 10.1007/s00395-019-0729-y. PMID: 30963299

Statin Use Improves Cardiometabolic Protection Promoted By Physical Training in an Aquatic Environment: A Randomized Clinical Trial

Rochelle Rocha Costa,[1] Alexandra Ferreira Vieira,[1] Leandro Coconcelli,[1] Alex de Oliveira Fagundes,[1] Adriana Cristine Koch Buttelli,[1] Laura Frances Pereira,[1] Ricardo Stein,[1,2] Luiz Fernando Martins Kruel[1]

Universidade Federal do Rio Grande do Sul,[1] Porto Alegre, RS - Brazil

Hospital de Clínicas de Porto Alegre,[2] Porto Alegre, RS - Brazil

Abstract

Background: **Statin use is highlighted as the most commonly utilized therapy for the treatment of dyslipidemias and can be considered as the most efficient pharmacological intervention for low-density lipoprotein (LDL) reduction. On the other hand, physical training can be considered an efficient and safe non-pharmacological strategy to promote improvements in lipid profile. However, the influence of statins on lipid adaptations arising from water-based training in populations with dyslipidemia is not known.**

Objectives: **To analyze the influence of simvastatin use on lipid adaptations arising from water-based aerobics and resistance training in elderly women with dyslipidemia.**

Methods: **Sixty-nine elderly (66.13 ± 5.13 years), sedentary, and dyslipidemic women, both non-users and users of simvastatin (20 mg and 40 mg), were randomized into the following 3 groups: water-based aerobic training (WA), water-based resistance training (WR), and control group (CG). Total duration of interventions, for all experimental groups consisted of 10 weeks, with 2 weekly sessions. Biochemical analyses were performed before the beginning of the interventions and repeated after the end of the trial. Generalized estimating equations were used to compare these data, setting $\alpha = 0.05$.**

Results: **In intention-to-treat analysis, the medicated participants obtained a greater magnitude of decrease in total cholesterol (TC) (-3.41 to -25.89 mg.dl^{-1}; $p = 0.038$), LDL (-5.58 to -25.18 mg.dl^{-1}; $p = 0.007$) and TC/HDL ratio (-0.37 to -0.61; $p = 0.022$) when compared to the non-medicated participants, and this decrease was statistically significant only in the WR group.**

Conclusions: **Statin use enhances the adaptations promoted by water-based physical training in CT, LDL levels, and CT/HDL ratio, and it is more pronounced after WR.**

Keywords: **Metabolic Syndrome/complications; Hydroxymethylglutaryl-CoA-Reductases Inhibitors; Exercise; Aquatic Environment; Physical Activity; Hypertension; Obesity; Diabetes Mellitus.**

Introduction

Dyslipidemias are lipid metabolism disorders resulting in altered blood lipoproteins and lipids.[1] In elderly women, reduced estrogen levels, which accompany post-menopause, can favor the development of dyslipidemia and contribute to increased cardiovascular risk.[2]

Statin therapy is the most commonly used treatment, and it is considered the most efficient pharmacological intervention for low-density lipoprotein (LDL) reduction.[3,4] However, several adverse events are associated with its use, including myopathy, which arises as a concerning side-effect.[5] However, physical training is considered an efficient and safe non-pharmacological strategy for the treatment of dyslipidemias.[3] Several studies demonstrate favorable adaptations in lipids and lipoproteins in response to aerobic[6-9] and resistance training.[10-12] Nevertheless, evidence suggests that statins can attenuate the improvements resulting from exercise training in some physical fitness components, such as cardiorespiratory conditioning[13] and muscle strength,[14] although these results are conflicting.[4]

It is well documented that isolated treatment with statins or physical training can promote lipid profile improvements,[3] but there are few studies assessing their associated effects. Coen et al.[15] demonstrated that 10 weeks of combined training (aerobic and resistance) combined with daily use of rosuvastatin did not alter lipids, compared to statin use alone. It is important to emphasize that this

Maling Address: Rochelle Rocha Costa •
Universidade Federal do Rio Grande do Sul Rua Felizardo, 750. Postal Code 90690-200, Porto Alegre, RS Brazil
E-mail: rochellerochacosta@msn.com
Manuscript received March 12, 2020, revised manuscript June 10, 2020, accepted August 05, 2020

DOI: https://doi.org/10.36660/abc.20200197

study did not include a group with only physical training; therefore, its isolated effects were not investigated.

In contrast, Wittke[16] compared the effects of aerobic training with or without fluvastatin use on lipid parameters of men with dyslipidemia. Both strategies improved lipid outcomes, but combined aerobic training and statin use was more efficient in reducing total cholesterol (TC) and LDL concentrations.

Water-based exercises performed in the orthostatic position are among the most prescribed exercise modalities for the elderly.[17,18] Specific physiological adaptations which arise from immersion lead to lower joint impact;[19] lower blood pressure;[20] greater systolic volume, cardiac output, and oxygen consumption;[20] suppression of the renin-angiotensin system;[21,22] greater release of natriuretic peptide; and increased oxidative capacity.[23,24] These adaptations result in important benefits for elderly patients and patients with dyslipidemias.

It is, therefore, relevant to know the effects of aerobic and resistance training in elderly patients with dyslipidemia. To the best of our knowledge, there are no studies investigating the influence of simvastatin on lipid adaptations promoted by water-based physical training in this population. Thus, this study aimed to analyze the influence of simvastatin use on lipid adaptations arising from water-based aerobic and resistance training in elderly women with dyslipidemia. We hypothesized that participants receiving statin would show greater magnitude of improvement in TC, triglycerides (TG), and LDL concentrations than those who did not receive statins.

Methods

Sample

The sample comprised 69 elderly (66.13 ± 5.13 years), sedentary (without regular physical activities for at least 3 months), dyslipidemic (TC > 200 mg.dl^{-1}, LDL ≥ 130 mg.dl^{-1}, TG ≥ 150 mg.dl^{-1}, or high-density lipoprotein [HDL] < 40 mg.dl^{-1}, isolated or combined),[3] non-smoking women. In order to assess the influence of statin use on lipid adaptations to physical training, women who were not receiving medication to treat dyslipidemias and women who were receiving simvastatin in dosages of 20 mg and 40 mg were accepted to compose the non-medicated group (NMED) and the medicated group (MED), respectively. Participants were recruited in December 2015, and they were randomly assigned into the following 3 groups: water-based aerobic training (WA; n = 23; 10 MED and 13 NMED), water-based resistance training (WR; n = 23; 9 MED and 14 NMED), and control (CG; n = 23; 9 MED and 14 NMED). All participants were instructed not to change their dietary habits and not to include additional exercise beyond that prescribed in the water-based interventions.

Participants were allocated into the 3 study groups by stratified randomization using a computer-generated random list. The baseline TC value was used as factor for the randomization process. Allocation concealment was performed by sequential, numbered, opaque and sealed envelopes. This procedure was performed by a blinded researcher, in order to maintain the confidentiality of allocation. The process of randomization and allocation were carried out after the completion of initial assessments.

This study was conducted according to the Declaration of Helsinki, and it received approval from the Ethics Committee of the Hospital de Clínicas de Porto Alegre (protocol 140547). All participants read and signed an informed consent form before starting their participation in the study. All the evaluations and the training sessions were performed from December 2015 to April 2016, at the Escola de Educação Física, Fisioterapia e Dança of Universidade Federal do Rio Grande do Sul and at Hospital de Clínicas de Porto Alegre. This trial has been registered at Clinical Trials (protocol NCT02900612.).

Study Design

This study was designed as a 3-arm randomized controlled clinical trial in parallel, with allocation ratio of 1:1:1. No changes were made to the methods after trial commencement. Biochemical analyses were used to measure TC, LDL (primary outcomes), TG, HDL levels, and the TC/HDL ratio (secondary outcomes). In order to identify the dietary habits of the participants, a 3-day dietary record was adopted. These measurements were performed before the beginning of the interventions and repeated 72 hours after the conclusion of the 10-week period. Prior to the beginning of the experimental protocols, anthropometric measurements were carried out to characterize the sample.

Dietary Record

To ensure that the participants did not alter their dietary habits, a dietary record of 3 different days was conducted to monitor eating habits. This instrument was completed by the participants themselves, and data were calculated adopting the nutrition software Diet Win Professional (Brubins CAS, Brazil). Carbohydrate (CHO), protein (PTN) and lipid (LIP) content were expressed as percentages of the daily total energy value (TEV).

Biochemical Assessments

After a 12-hour fasting period, 4 ml of blood were taken from the antecubital vein. Samples were centrifuged at 1,500 rpm for 20 minutes and the extracted plasma was stored at −80 °C (ultra freezer NUAIRE, Plymouth, USA). A researcher who was blinded to the experimental conditions conducted the lipid profile analysis. TC, TG, and HDL were analyzed by enzymatic method using kits from Siemens (Caernarfon, USA) and a Siemens Advia 1800 automated chemistry analyzer (Erlangen, Germany). Based on these values, LDL levels were estimated according to Friedewald et al.,[25] and the TC/HDL ratio was calculated.

Aquatic Incremental Test

The incremental test was performed to determine the heart rate corresponding to the anaerobic threshold (HR_{AT}), which was used as an indicator of the intensity of aerobic training, adopting the stationary running exercise. The test was performed prior to the training sessions, and it was repeated

in the fifth training week in order to readjust this parameter. The incremental test has been described in detail in the study by Alberton et al.[19] HR_{AT} determination was carried out by 3 independent, blinded, experienced exercise physiologists. Disagreements were decided by consensus.

Aquatic Interventions

Before training sessions begins, individuals who participated in the WA and WR groups held 2 familiarization sessions with the aquatic exercises utilized in the training program, in order to ensure proper execution of the movements. Total duration of interventions for all experimental groups consisted of 10 weeks, with 2 weekly sessions, resulting in a total of 20 sessions.

Training of WA and WR groups was changed after 5 weeks in order to increase the intensity. The training sessions of these groups comprised the same general structure, with a total duration of 45 minutes, each divided as follows: warm-up (8 minutes), main part (approximately 30 minutes) and cool-down (7 minutes).

Interval training was adopted for WA group, with intensities ranging from 90% to 100% of the HR_{AT} for what we called "stimulus period" and 80% to 90% of the HR_{AT} for recovery. Six blocks of 5 minutes were performed, in which 4 minutes were intended for training stimulus, and the other 1 minute to recovery. In the first 5 weeks, we adopted 4 minutes at an intensity corresponding to HR ranging between 90% and 95% of the HR_{AT}, interspersed by 1 minute between 80% and 85% HR_{AT}; for the last 5 weeks the subjects trained for 4 minutes between 95% and 100% of the HR_{AT} and for 1 minute between 85% and 90% of the HR_{AT} during recovery. The training intensity control of WA group was conducted using HR monitors (POLAR, FT1, Finland).

During the whole training period, the WR group performed the exercises adopting the maximum execution speed of the movements. They also kept a fixed time of 1 minute and 20 seconds for each exercise. The intervals between the sets were active and performed at a very light self-selected intensity. During the first 5 weeks, 4 sets of 20 seconds were performed, with recovery intervals of 2 minutes and 45 seconds between sets. During the following 5 weeks, 8 sets of 10 seconds were accomplished with intervals of 1 minute and 40 seconds between the sets. The exercises performed by the participants of the WA and WR groups were described in detailed by Costa et al.[26].

CG participants performed a non-periodized program comprising relaxation exercises in immersion, in order to maintain the same weekly immersion amount of the WA and WR participants, with the aim of matching the physiological effects of immersion on lipid outcomes for the 3 experimental groups.

Statistical Analysis

The sample size was determined using GPower software (version 3.1, Universität Düsseldorf, Germany) for a power of about 0.80 (significance level of 0.05 and correlation coefficient of 0.8), based on data from research by Volaklis, Spassis, and Tokmakidis [7] and Takeshima et al.[17] This calculation showed that 19 women would be needed in each group.

Shapiro-Wilk and Levene tests were adopted for analysis of the normality and homogeneity of the data, respectively. One-way analysis of variance (for scalar variables) and chi-square test (for categorical variables) were performed to compare data from the 3 groups (WA, WR, and CG) at baseline (sample characterization). These data were shown as means and 95% confidence intervals.

Generalized estimating equations (GEE) and Bonferroni post hoc tests were used to compare the data of all dependent variables (primary and secondary outcomes) and of the dietary recalls. Thus, the factors adopted in this analysis were "group" (WA, WR, and CG) and "medication status" (medicated and non-medicated). These data were presented as mean difference (post-intervention minus pre-intervention values) and 95% confidence intervals, in intention-to-treat analysis. Furthermore, the effect size (Cohen's d) was calculated from mean differences values between WA and WR *versus* CG, and classified as small (between 0.2 and 0.5), moderate (between 0.5 and 0.8), or large (0.8 or more).[27] These results were shown as means and 95% confidence interval. For all analyses, significance level was set at $\alpha = 0.05$, and the statistical software SPSS (Statistical Package for Social Sciences for Mac, version 22.0, IBM, USA) was used.

Results

Although the experiment started with 69 women randomly assigned to WA (n = 23), WR (n = 23), and CG (n = 23), 7 participants withdrew from the study during the intervention period (3 from WA and 4 from CG), representing a dropout of 10%. Thus, 62 participants finished the study interventions and completed all assessments (Figure 1). The participants who completed the intervention had an attendance frequency above 95%, demonstrating adherence to training. Sample baseline characteristics are presented in Table 1.

Considering the dietary record, there were no significant effects of group (TEV $p = 0.938$; CHO $p = 0.872$; PTN $p = 0.911$; LIP $p = 0.899$) or time (TEV $p = 0.708$; CHO $p = 0.790$; PTN $p = 0.799$; LIP $p = 0.819$) and no significant interactions between these factors (TEV $p = 0.803$; CHO $p = 0.801$; PTN $p = 0.873$; LIP $p = 0.858$).

Significant effects were found in factor of group for all outcomes analyzed in the present study (TC: $p < 0.001$; TG: $p < 0.001$; LDL: $p < 0.001$; HDL: $p < 0.001$; TC/HDL ratio: $p < 0.001$), indicating that WA, WR, and CG showed distinct alterations resulting from trainings for each outcome. Bonferroni test evidenced a statistically different behavior between the CG and the WA and WR groups, without difference between the groups with physical training (WA and WR). For the outcomes of TC, TG, LDL, HDL, and TC/HDL ratio, the CG presented mean differences with the opposite behavior of those observed in the 2 other groups; that is, when WA and WR groups showed decreases in the outcomes, CG showed an increase (TC, TG, LDL, and TC/HDL ratio), and when WA and WR groups showed increases in the outcomes, CG showed a decrease (HDL) (Figure 2).

On the other hand, significant effects for the factor of medication were only found for the outcomes of TC (p = 0.038), LDL (p = 0.007), and TC/HDL ratio (p = 0.022). The Bonferroni test demonstrated that only WR group participants showed improvements of different magnitudes, depending on their medication status. The medicated participants obtained a decrease of greater magnitude in TC, LDL, and TC/HDL ratio when compared to the non-medicated ones. Significant interactions between group and medication status were not observed for TC (p = 0.100), TG (p = 0.153), LDL (p = 0.171), HDL (p = 0.083) and TC/HDL ratio (p = 0.815) (Figure 2).

The analysis of the effect size, comparison of the participants of WA and CG showed a large magnitude of effect for all the outcomes. Similarly, a large magnitude of effect was observed in the comparison of participants of WR and CG, regardless of medication status (Table 2).

Discussion

The main finding of the present study refers to the positive influence of statin use on the adaptations arising from WR, maximizing its beneficial effects on TC, LDL, and TC/HDL ratio levels. Therefore, the hypothesis that the medicated participants would show improvements of greater magnitudes in TC and LDL outcomes, regardless of the training model, was partially confirmed.

The additive effects on the benefits of physical training in TC, LDL, and TC/HDL ratio induced by statins can be explained by its mechanism of action. These drugs are composed by hydroxymethylglutaryl-coenzyme A (HMG CoA) reductase inhibitors. This inhibition results in intracellular cholesterol reduction, and, thus, a greater stimulus to the increase of the synthesis and expression of LDL receptors, resulting in increased capture of circulating cholesterol.[28]

The effects of physical training associated to the use of statins on lipid profile were previously investigated in the dyslipidemic population. Coen et al.[15] evaluated the addition of a combined physical training program to the daily use of rosuvastatin (10 mg), during 10 weeks in sedentary individuals of both sexes. The study showed a decreasing tendency in TC and LDL levels and an increase in HDL levels in those enrolled to exercise plus rosuvastatin. However, it is not possible to compare the results from Coen et al.[15] with those found in the present study, since they did not evaluate a group that performed only exercise. Nevertheless, Wittke[16]

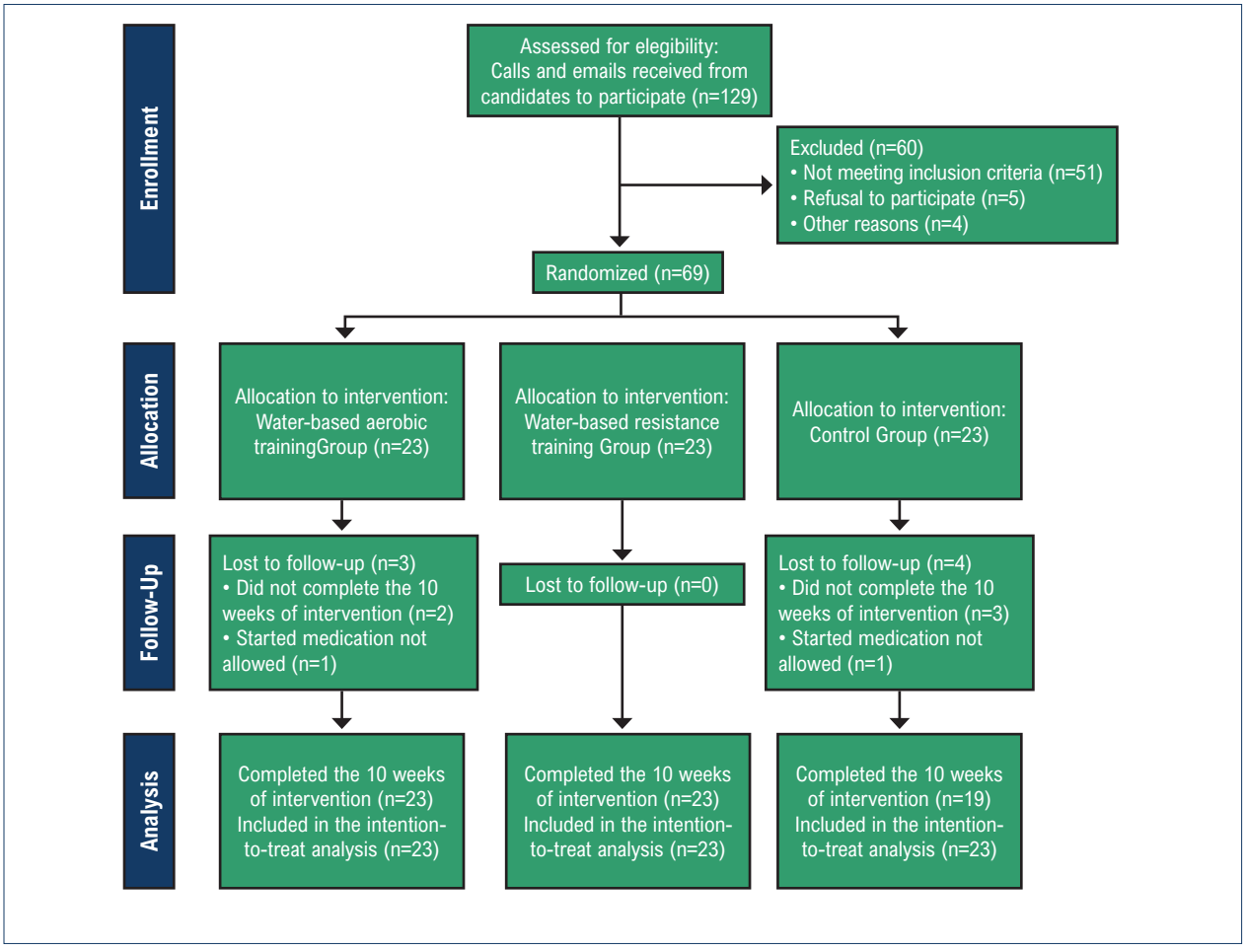


Figure 1 – *Flow diagram showing the participants enrollment process, allocation, follow-up and analysis.*

Table 1 – Baseline characteristics of the water-based aerobic trainings (WA), water-based resistance traininge (WR) and control (CG) groups

	WA (n=23) Mean ± SD (95% CI)	WR (n=23) Mean ± SD (95% CI)	CG (n=23) Mean ± SD (95% CI)	p value
Age (years)	66.80 ± 5.51 (64.55 to 69.05)	66.78 ± 5.80 (64.41 to 69.15)	64.63 ± 5.87 (62.23 to 67.03)	0.316
Body weight (kg)	71.18 ± 11.40 (66.52 to 75.84)	71.51 ± 15.72 (65.09 to 77.94)	76.91 ± 17.79 (69.64 to 84.18)	0.168
Height (m)	1.57 ± 0.06 (1.55 to 1.60)	1.55 ± 0.06 (1.52 to 1.57)	1.58 ± 0.07 (1.55 to 1.61)	0.825
BMI (kg.m^{-2})	28.83 ± 4.20 (27.12 to 30.55)	29.88 ± 6.04 (27.41 to 32.35)	30.91 ± 6.95 (28.07 to 33.75)	0.207
Statin use (n/%)	10/43	9/39	9/39	0.639
Statin 20 mg use (n/%)	5/22	4/17	4/17	0.961
Statin 40 mg use (n/%)	5/22	5/22	5/22	0.961

BMI: body mass index; CI: Confidence interval. P values were obtained from one-way analysis of variance (scalar variables) and chi-square test (categorical variables).

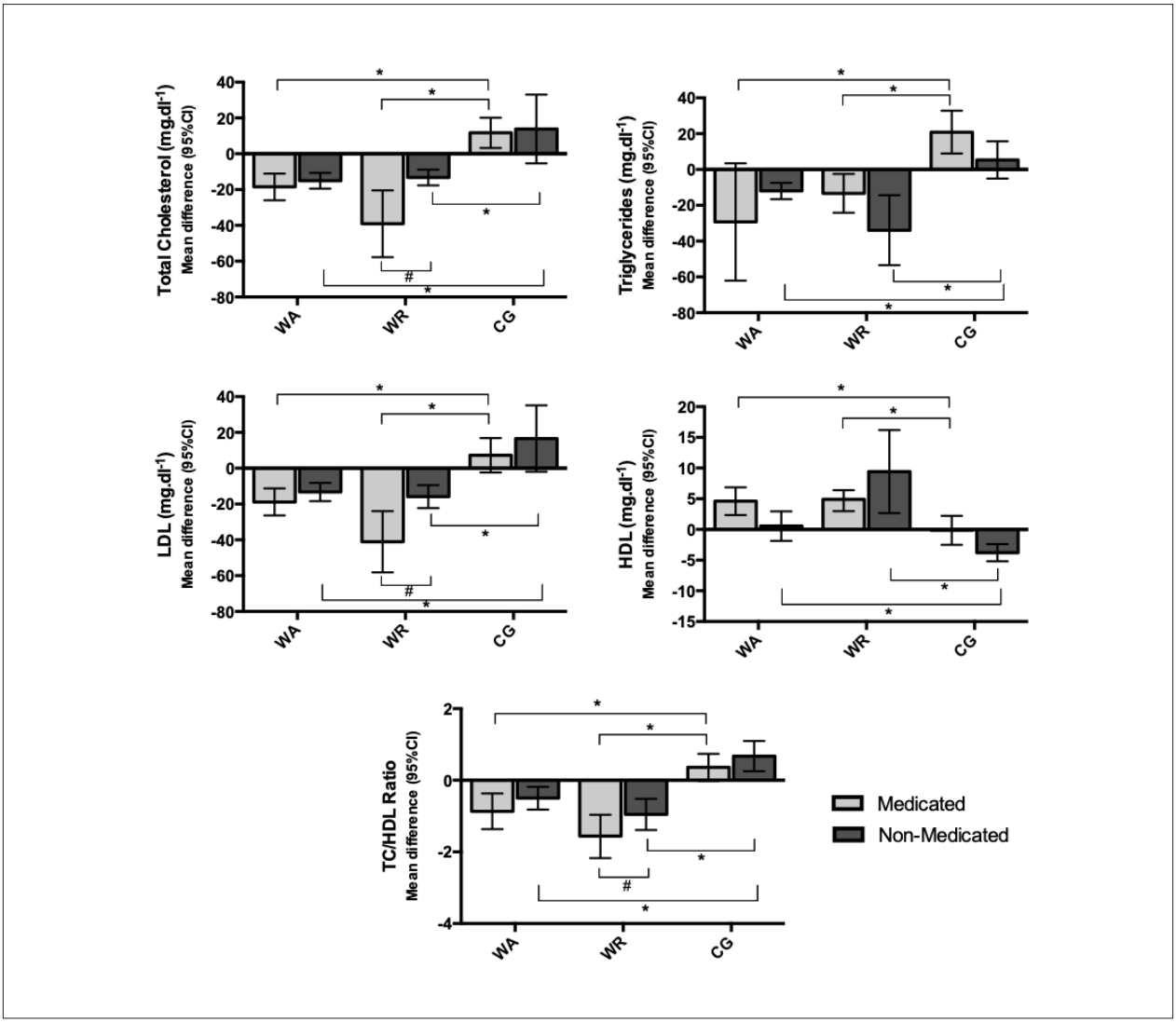


Figure 2 – *Mean difference (change from baseline) and 95% confidence interval of blood concentrations of total cholesterol (TC) (A), triglycerides (TG) (B), low-density lipoprotein (LDL) (C), high-density lipoprotein (HDL) (D) and TC/HDL ratio (E) of water-based aerobic training (WA), water-based resistance training (WR) and control group (CG) participants medicated and non-medicated with statin. * Indicates statistically significant difference from the WR group with the same medication status. ** Indicates statistically significant difference from the other 2 groups with same medication status. # Indicates statistically significant difference between medication status within the same group. Statistical differences were obtained from generalized estimating equations and Bonferroni post hoc tests.*

Table 2 – Effect size of the water-based aerobic training (WA) versus control group (CG) and water-based resistance training (WR) versus control group, in medicated and non-medicated participants

	Medicated participants		Non-medicated participants	
Outcome	WA versus CG Effect size (95% CI)	WR versus CG Effect size (95% CI)	WA versus CG Effect size (95% CI)	WR versus CG Effect size (95% CI)
TC	1.52 (0.87 a 2.18)	1.41 (0.77 a 2.06)	0.83 (0.23 a 1.44)	0.78 (0.18 a 1.38)
TG	0.82 (0.22 a 1.42)	1.20 (0.57 a 1.83)	0.87 (0.27 a 1.47)	1.01 (0.39 a 1.62)
HDL	0.87 (0.27 a 1.47)	0.94 (0.33 a 1.55)	0.89 (0.28 a 1.49)	1.09 (0.47 a 1.71)
LDL	1.22 (0.59 a 1.84)	1.40 (0.76 a 2.04)	0.88 (0.28 a 1.49)	0.94 (0.33 a 1.55)
TC/HDL	1.12 (0.50 a 1.74)	1.53 (0.87 a 2.18)	1.25 (0.62 a 1.88)	1.52 (0.86 a 2.17)

HDL: high-density lipoprotein; LDL: low-density lipoprotein; TC: total cholesterol; TG: triglycerides.

demonstrated that a moderate intensity aerobic exercise program, twice a week during 3 months, was able to promote positive adaptations in lipid profile outcomes, mainly TG (-68.00 mg.dl^{-1}) and HDL ($+7.70$ mg.dl^{-1}). When this model of physical training was associated with the previous use of fluvastatin (20 mg/day), similar effects were found in the group that performed only physical training and the group that already used the medicine prior to the beginning of the protocol. On the other hand, alterations with marked magnitudes in all lipid profile outcomes were found in the group that begun the drug treatment simultaneously to aerobic training. However, there were significant differences only in TC and LDL in relation to the group that performed isolated training. These results corroborate the findings of the present study, where the medicated participants started the training protocols while already receiving treatment with simvastatin, and those who performed water-based aerobic training did not show alterations with significant magnitudes in the studied variables, when compared with the participants from the group that did not use medication.

It is important to mention that our findings also demonstrate that both water-based training models (WA and WR) promote improvements in the lipid profile of elderly women with dyslipidemia, confirming our initial hypothesis. The improvements occurred in a similar manner among the participants that underwent aerobic training and those who performed resistance training, thus showing efficacy of the prescription and periodization of the proposed protocols.

Lipid profile results of the proposed trainings corroborate the literature that demonstrated that water aerobics and water resistance exercises are efficient in promoting improvements in these parameters.[7,10,17,29-35] Studies suggest that the main explanatory mechanisms for these findings are related to lipoprotein lipase, cholesteryl ester transfer protein, lecithin cholesterol acyltransferase, hepatic lipase, and phospholipase A2 optimization with training.[36-37]

More specifically regarding the aquatic environment, the literature points out that simple immersion in orthostatic position promotes (or causes) the suppression of the rennin-angiotensin system,[21,22] which leads to an increased blood volume, and consequent increase in the distensibility of cardiac chambers.[38] This is a stimulus for the reduction in circulating levels of vasoconstrictor hormones, such as norepinephrine and vasopressin, in addition to the decrease of plasmatic renin activity.[39] Consequently, the need for increased secretion and release of atrial natriuretic peptide (ANP) is signaled, which, in fact, presents high concentrations in both situations of immersion at rest and in the performance of exercises in aquatic environments.[35,40,41] Interestingly, Engeli et al.[24] claim that the activation of ANP signaling contributes to the increase of lipid oxidative capacity, influencing the choice of substrates for energy production during exercise. According to Moro and Smith,[23] ANP is a powerful regulator of lipid metabolism, especially in the accomplishment of exercises in immersion. Its activation is involved in a cascade of enzymatic reactions of the hormone-sensitive lipase and lipoprotein lipase, which directly act on the modulation of blood lipid concentrations. It is postulated that this might represent an explanatory route for the beneficial findings in regard to water-based exercise protocols in the lipid profile of patients with dyslipidemia. However, although its effect has been reported in the literature, it seems that immersion alone (at rest, with no additional effect of exercise) was not efficient to promote improvements in the lipids of CG participants of the present study.

This study has some limitations. First, the sample was composed exclusively of elderly women; therefore, the results cannot be extrapolated to men or younger women. Second, it was not known for how long simvastatin was used by the entire sample prior to the experiment entry, and other simvastatin doses (10 or 80 mg) were not tested. Since the dosage of the experimental drug was intermediate and its efficacy has been shown to be lower in comparison to "newer" statins, the effect of 80 mg of simvastatin or the prescription of another statin (atorvastatin, rosuvastatin, or pitavastatin) may provide a more positive effect on the lipid profile of the sample.[42] Finally, for financial reasons, ANP concentrations and the activity of lipid metabolism enzymes were not tested. These analyses could provide a comprehensive overview of the real mechanisms by which lipid profile is altered, as a result of different water-based training models. However, our goal was not to develop a mechanistic study, but to evaluate the influence of simvastatin in lipid adaptations arising from water-based training in a specific sample with dyslipidemia.

Conclusions

Non-medicated dyslipidemic or simvastatin-intolerant elderly women can adopt water-based physical training

as a treatment tool to improve lipid profile. On the other hand, elderly female patients with dyslipidemia who are on simvastatin, but persist with uncontrolled levels of TC and LDL can also benefit from the effects of water-based aerobic and resistive training, enhancing the drug's lipid-lowering effect.

Acknowledgments

This research was supported by the Fundo Incentivo à Pesquisa e Eventos from Hospital de Clínicas de Porto Alegre. No potential conflicts of interest relevant to this article were reported.

Author Contributions

Conception and design of the research: Costa RR, Stein R, Kruel LFM; Acquisition of data: Vieira AF, Coconcelli L, Fagundes AO, Pereira LF; Analysis and interpretation of the data: Costa RR, Vieira AF, Coconcelli L, Fagundes AO, Buttelli ACK, Stein R, Kruel LFM; Statistical analysis: Costa RR, Kruel LFM; Obtaining financing: Stein R, Kruel LFM; Writing of the manuscript: Costa RR, Vieira AF, Coconcelli L, Buttelli ACK, Pereira LF, Stein R, Kruel LFM; Critical revision of the manuscript for intellectual contente: Costa RR, Vieira AF, Fagundes AO, Stein R, Kruel LFM.

Potential Conflict of Interest

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

Sources of Funding

This study was partially funded by FIPE/HCPA.

Study Association

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

References

1. Gau GT, Wright RS. Pathophysiology, diagnosis and management of dyslipidemia. *Curr Probl Cardiol*. 2006;31(7):445-86. doi:10.1016/j.cpcardiol.2006.03.001.
2. Casanova G, Ramos RB, Ziegelmann P, Spritzer PM. Effects of low-dose versus placebo or conventional-dose postmenopausal hormone therapy on variables related to cardiovascular risk: a systematic review and meta-analysis of randomized clinical trials. *J Clin Endocrinol Metab*. 2015;100(3):1028–37. doi:10.1210/jc.2014-3301.
3. National Cholesterol Education Program (NCEP). Third report of the expert panel on detection, evaluation, and treatment of high blood cholesterol in adults. Bethesda, MD: National Heart, Lung, and Blood Institute; 2002.
4. Murlasits Z, Radák, Z. The effects of statin medications on aerobic exercise capacity and training adaptations. *Sports Med*. 2014;44(11):1519-30. doi:10.1007/s40279-014-0224-4.
5. Ahmad Z. Statin intolerance. *Am J Cardiol*. 2014;113:1765-71. doi:org/10.1016/j.amjcard.2014.02.033.
6. Durstine JL, Grandjean PW, Davis PG, Ferguson MA, Alderson NL, DuBose KD. Blood lipid and lipoprotein adaptations to exercise: a quantitative analysis. *Sports Med*. 2001;31(15):1033-62.
7. Volaklis KA, Spassis AT, Tokmakidis SP. Land versus water exercise in patients with coronary artery disease: Effects on body composition, blood lipids, and physical fitness. *Am Heart J*. 2007;154(3):560.e1-6. doi:10.1016/j.ahj.2007.06.029.
8. Halverstadt A, Phares DA, Wilund KR, Goldberg AP, Hagberg JM. Endurance exercise training raises high-density lipoprotein cholesterol and lowers small low-density lipoprotein and very low-density lipoprotein independent of body fat phenotypes in older men and women. *Metabolism*. 2007;56(4):444–50. doi:10.1016/j.metabol.2006.10.019.
9. Coghill N, Cooper AR. The Effect of a home-based walking program on risk factors for coronary heart disease in hypercholesterolaemic men. A randomized controlled trial. *Prev Med*. 2008;46(6):545-551. doi:10.1016/j.ypmed.2008.01.002.
10. Colado JC, Triplett NT, Tella V, Saucedo P, Abellán J. Effects of aquatic resistance training on health and fitness in postmenopausal women. *Eur J Appl Physiol*. 2009;106(1):113-122. doi:10.1007/s00421-009-0996-7.
11. Kelley GA, Kelley KS. Impact of progressive resistance training on lipids and lipoproteins in adults: A meta-analysis of randomized controlled trials. *Prev Med*. 2009;48(1):9-19. doi:10.1016/j.ypmed.2008.10.010.
12. Costa RR, Alberton CL, Tagliari M, Kruel LFM. Effects of resistance training on the lipid profile in obese women. *J Sports Med Phys Fitness*. 2011;51(1):169-77.
13. Mikus CR, Boyle LJ, Borengasser SJ, Oberlin DJ, Naples SP, Fletcher J, et al. Simvastatin impairs exercise training adaptations. *J Am Coll Cardiol*. 2013;62(8):709-14. doi:10.1016/j.jacc.2013.02.074.
14. Loenneke JP, Loprinzi PD. Statin use may reduce lower extremity peak force via reduced engagement in muscle-strengthening activities. *Clin Physiol Funct Imaging*. 2016;1-4. doi:10.1111/cpf.12375.
15. Coen, PM, Flynn MG, Markofski MM, Pence BD, Hannemann RE. Adding exercise training to rosuvastatin treatment: influence on serum lipids and biomarkers of muscle and liver damage. *Metabolism*. 2009;58(7):1030-8. doi:10.1016/j.metabol.2009.03.006.
16. Wittke R. Effect of fluvastatin in combination with moderate endurance training on parameters of lipid metabolism. *Sports Med*. 1999;27(5):329-335.
17. Takeshima N, Rogers ME, Watanabe E, Brechue WF, Okada A, Yamada T, et al. Water-based exercise improves health-related aspects of fitness in older women. *Med Sci Sports Exerc*. 2002;34(3):544-51.
18. Kanitz AC, Delevatti RS, Reichert T, Liedtke GV, Ferrari R, Almada BP, et al. Effects of two deep water training programs on cardiorespiratory and muscular strength responses in older adults. *Exp Gerontol*. 2015;64:55-61. doi:10.1016/j.exger.2015.02.013.
19. Alberton CL, Antunes AH, Beilke DD, Pinto SS, Kanitz AC, Tartaruga MP, et al. Maximal and ventilatory thresholds of oxygen uptake and rating of perceived exertion responses to water aerobic exercises. *J Strength Cond Res*. 2013;27(7):1897-903. doi:10.1519/JSC.0b013e3182736e47.
20. Pendergast DR, Moon RE, Krasney JJ, Held HE, Zamparo P. Human physiology in an aquatic environment. *Compr Physiol*. 2015;5(4):1705-50. doi:10.1002/cphy.c140018.
21. Pump B, Shiraishi M, Gabrielsen A, Bie P, Christensen NJ, Norsk P. Cardiovascular effects of static carotid baroreceptor stimulation during water immersion in humans. *Am J Physiol Heart Circ Physiol*. 2001;280(6):H2607-H2615.

22. Schou M, Gabrielsen A, Bruun NE, Skott P, Pump B, Dige-Petersen H, et al. Angiotensin II attenuates the natriuresis of water immersion in humans. *Am J Physiol Regul Integr Comp Physiol*. 2002; 283(1):R187–R196. doi:10.1152/ajpregu.00536.2001.

23. Moro C, Smith SR. Natriuretic peptides: new players in energy homeostasis. *Diabetes*. 2009;58(12):2726-8. doi:10.2337/db09-1335.

24. Engeli S, Birkenfeld AL, Badin PM, Bourlier V, Louche K, Viguerie N, et al. Natriuretic peptides enhance the oxidative capacity of human skeletal muscle. *J Clin Invest*. 2012;122(12):4675-9. doi:10.1172/JCI64526.

25. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem*. 1972;18(6):498-502.

26. Costa RR, Kanitz AC, Reichert T, Prado AKG, Coconcelli L, Buttelli ACK, et al. Water-based aerobic training improves strength parameters and cardiorespiratory outcomes in elderly women. *Exp Gerontol*. 2018;108:231-9. doi:10.1016/j.exger.2018.04.022

27. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2 ed. New York: Laurence Erlbaum Associates;1988.

28. Chan DC, Watts GF, Barret HR, Mori TA, Beilin LJ, Redgrave TG. Mechanism of action of a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor on apolipoprotein B-100 kinetics in visceral obesity. *J Clin Endocrinol Metab*. 2002;87(5):2283–9. doi:10.1210/jcem.87.5.8455.

29. Pechter U, Maaroos J, Mesikepp S, Veraksits A, Ots M. Regular low-intensity aquatic exercise improves cardiorespiratory functional capacity and reduces proteinuria in chronic renal failure patients. *Nephrol Dial Transplant*. 2003;18(3):624-5.

30. Asa C, Maria S, Katharina SS, Bert A. Aquatic exercise is effective in improving exercise performance in patients with heart failure and type 2 diabetes mellitus. *Evid Based Complement Alternat Med*. 2012. doi:10.1155/2012/349209.

31. Ayaz A, Roshan VD. Effects of 6-week water-based intermittent exercise with and without Zingiber Officinale on pro-inflammatory markers and blood lipids in overweight women with breast cancer. *J Appl Pharm Sci*. 2012;02(05):218-24.

32. Greene NP, Martin SE, Crouse SF. Acute exercise and training alter blood lipid and lipoprotein profiles differently in overweight and obese men and women. *Obesity*. 2012;20(8):1618-27. doi:10.1038/oby.2012.65.

33. Arca EA, Martinelli B, Martin LC, Waisberg CB, Franco RJS. Aquatic exercise is as effective as dry land training to blood pressure reduction in postmenopausal hypertensive women. *Physiother Res Int*. 2014;19(2):93-8. doi:10.1002/pri.1565.

34. Kasprzak Z, Pilaczyńska-Szcześniak L. Effects of regular physical exercises in the water on the metabolic profile of women with abdominal obesity. *J Hum Kinet*. 2014;41:71-9. doi:10.2478/hukin-2014-0034.

35. Delevatti, RS, Kanitz AC, Alberton CL, Marson EC, Lisboa SC, Pinho CD, et al. Glucose control can be similarly improved after aquatic or dry-land aerobic training in patients with type 2 diabetes: A randomized clinical trial. *J Sci Med Sport*. 2016;19(8):688-693. doi:10.1016/j.jsams.2015.10.008.

36. Kuivenhoven JA, Pritchard H, Hill J, Frohlich J, Assmann G, Kastelein J. The molecular pathology of lecithin:cholesterol acyltransferase (LCAT) deficiency syndromes. *J Lipid Res*. 1997;38(2):191-205.

37. Deeb SS, Zambon A, Carr MC, Ayyobi AF, Brunzell JD. Hepatic lipase and dyslipidemia: interactions among genetic variants, obesity, gender, and diet. *J Lip Res*. 2003;44(7):1279-86. doi:10.1194/jlr.R200017-JLR200.

38. Moro C, Pillard F, De Glisezinski I, Harant I, Rivière D, Stich V, et al. Training enhances ANP lipid-mobilizing action in adipose tissue of overweight men. *Med Sci Sports Exerc*. 2005;37(7):1126–1132. doi:10.1249/01.mss.0000170124.51659.52.

39. Shiraishi M, Schou M, Gybel M, Christensen NJ, Norsk P. Comparison of acute cardiovascular responses to water immersion and head-down tilt in humans. *J Appl Physiol*. 2002;92(1):264-8.

40. Nagashima K, Nose H, Yoshida T, Kawabata T, Oda Y, Yorimoto A, et al. Relationship between atrial natriuretic peptide and plasma volume during graded exercise with water immersion. *J Appl Physiol*. 1995;78(1):217–24.

41. Stocks JM, Patterson MJ, Hyde DE, Jenkins AB, Mittleman KD, Taylor NA. Effects of immersion water temperature on whole-body fluid distribution in humans. *Acta Physiol Scand*. 2004;182:3-10. doi:10.1111/j.1365-201X.2004.01302.x.

42. National Institute for Health and Care Excellence (NICE). Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Clinical guideline CG181: methods, evidence and recommendations BMJ.2014;349:g4356 doi: https//doi.org/10.1136/bmj.g4356

Statin Associated With Physical Training: A Perfect Combination

Stephanie Bastos da Motta,[1] Vanessa Caroline Toledes,[2] Leandro Franzoni[3]

Hospital de Clínicas de Porto Alegre - Grupo de Vascular e Exercício – VascuEx,[1] Porto Alegre, RS - Brazil

Faculdade Cenecista Santo Ângelo - Curso de Fisioterapia,[2] Santo Ângelo, RS - Brazil

Universidade Federal do Rio Grande do Sul – UFRGS,[3] Porto Alegre, RS - Brazil

Short Editorial related to the article: Statin Use Improves Cardiometabolic Protection Promoted By Physical Training in an Aquatic Environment: A Randomized Clinical Trial

Dyslipidemia and metabolic syndrome have grown exponentially over the recent years, including in children, mainly due to the low quality of food and the high level of a sedentary lifestyle.[1-3] These two diseases are important risk factors for the development of cardiovascular diseases.[4] Reduction of low-density lipoprotein (LDL), as well as total cholesterol (TC) and the TC to high-density lipoprotein ratio (HDL – TC/HDL) are the main forms of cardiometabolic prevention.[5] The use of statins is considered a standard treatment and the most effective pharmacological measure to improve the lipid profile.[6] However, there are non-pharmacological alternatives that are also effective, one of which is physical exercise.

There is evidence on the importance of regular physical training as a form of primary or secondary prevention in the development or worsening of cardiometabolic diseases.[7-9] However, there is no consensus on the effect of combining statins with physical training, two powerful tools that, combined, can promote an even greater impact on the lipid profile. This is what the Costa et al.[10] did in this edition of *Arquivos Brasileiros de Cardiologia* — they analyzed the influence of simvastatin on lipid adaptations resulting from aerobic and strength water training in elderly women with dyslipidemia. To this end, 69 female elderly sedentary dyslipidemic non-users and users of simvastatin (20 mg and 40 mg) (66.13±5.13 years) were analyzed.

Below are the main methodological points of the article: it is a randomized clinical trial with 3 groups (aerobic water training – WA; strength water training – WR; control group – CG). The intervention lasted 10 weeks (2 times a week) for all groups. The WA group included 23 women (10 using statin and 13 not using statin); the WR group consisted of 23 women (9 using statin and 14 not using statin); and the CG consisted of 23 women (9 not using statin and 14 not using statin). This is the first positive point of the study: well-executed randomization with equal sample n in all groups and correct distribution of statin use.

Regarding the water training program, participants of the WA and WR groups attended 2 induction sessions before the beginning of follow-up. Besides, exercise intensity was increased after 5 weeks of intervention. The exercise sessions lasted 45 minutes, including 8 minutes of warm-up, 30 minutes of exercise and 7 minutes of cool-down. For the WA group, interval training was adopted with an intensity of 90% to 100% of the heart rate corresponding to the anaerobic threshold (HR_{AT}). The WR group performed the exercises adopting a maximum execution speed, and maintained a fixed duration of 1 minute and 20 seconds for each exercise, while the CG performed a non-periodized program of immersion relaxation exercises in order to maintain the HART same number of weekly sessions as the other groups. The second merit of the study was to control exercise intensity by HR_{AT}, in addition to periodizing physical training, planning an increased intensity during follow-up.

Below are the main findings of the study: in summary, statin use associated with exercise training improves LDL, TC and TC/HDL. How much? Participants medicated for LDL: -5.58 to 25.18 $mg.dl^{-1}$; TC: -3.41 to 25.89 $mg.dl^{-1}$; TC/HDL: -0.37 to 0.61 $mg.dl^{-1}$, with significant p compared to non-medicated participants. This reduction is only statistically significant for the WR group. In general, the use of statins associated with strength water training seems to be the most effective strategy in reducing the lipid parameters evaluated in the study.

We are aware of the importance of aerobic physical training, especially for its protection against multiple cardiovascular risk factors. However, there is evidence suggesting that strength training is the most effective tool to improve the lipid profile, especially increasing HDL, and consequently reducing TC/HDL.[11] During clinical practice, specialists know that combined physical training, that is, aerobic and strength training together, in the same session or in different sessions, has benefits in several parameters and turns out to be the training style most used in professional daily life, adding up the benefits of aerobic exercise and strength exercise. The study has many merits, but we suggest future studies comparing the effect of combined training and studies on dyslipidemic men, including an expanded age range, as these study findings only apply to elderly women.

Keywords

Dyslipidemias/prevention and control; Metabolic Syndrome X; Hydroxymethylglutaril-CoA-Reductases; Risk Factors; Exercise; Sports; Swimming.

Mailing Address: Leandro Franzoni •
Universidade Federal do Rio Grande do Sul – UFRGS - Rua Itaboraí, 683. Postal Code 90040-060, Porto Alegre, RS – Brazil
E-mail: franzoni_77@hotmail.com

DOI: https://doi.org/10.36660/abc.20210509

Acknowledgements

To *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES)* for granting the doctoral scholarship and to the Health Sciences Program: Cardiology and Cardiovascular Sciences from Universidade Federal do Rio Grande do Sul for the job opportunity.

References

1. Saklayen MG. The Global Epidemic of the Metabolic Syndrome. Curr Hypertens Rep. 2018;20(2):12. doi: 10.1007/s11906-018-0812-z.
2. Gomes IL, Zago VHS, Faria EC. Avaliação de Perfis Lipídicos Infanto-Juvenis Solicitados nas Unidades Básicas de Saúde em Campinas/SP, Brasil: Um Estudo Laboratorial Transversal. Arq Bras Cardiol. 2020;114(1):47-56.
3. Reuter CP, Brand C, Silva PT, Reuter M, Renner JDP, Franke SIR, Mello ED, et al. Relação entre Dislipidemia, Fatores Culturais e Aptidão Cardiorrespiratória em Escolares. Arq Bras Cardiol. 2019;112(6):729-36.
4. Cesena FHY, Valente VA, Santos RD, Bittencourt MS. Risco Cardiovascular e Elegibilidade Para Estatina na Prevenção Primária: Comparação Entre a Diretriz Brasileira e a Diretriz da AHA/ACC. Arq Bras Cardiol. 2020;115(3):440-9.
5. Stein EA, Raal FJ. Lipid-Lowering Drug Therapy for CVD Prevention: Looking into the Future. Curr Cardiol Rep. 2015;17(11):104.
6. Furtado RHM, Genestreti PR, Dalçóquio TF, Baracioli LM, Lima FG, Franci A, Giraldez RRCV, et al. Associação entre Terapia com Estatinas e Menor Incidência de Hiperglicemia em Pacientes Internados com Síndromes Coronarianas Agudas. Arq Bras Cardiol. 2021;116(2):285-94.
7. Costa RR, Buttelli ACK, Coconcelli L, Pereira LF, Vieira AF, Fagundes AO, e al. Water-Based Aerobic and Resistance Training as a Treatment to Improve the Lipid Profile of Women With Dyslipidemia: A Randomized Controlled Trial. J Phys Act Health. 2019;16(5):348-54.
8. Brianezi L, Ornelas E, Gehrke FS, Fonseca FLA, Alves BCA, Sousa LVA, Souza J, et al. Efeitos do Treinamento Físico sobre o Miocárdio de Camundongos LDLr Knockout Ovariectomizadas: MMP-2 e -9, Colágeno I/III, Inflamação e Estresse Oxidativo. Arq Bras Cardiol. 2020;114(1):100-5.
9. Marongiu E, Crisafulli A. Cardioprotection acquired through exercise: the role of ischemic preconditioning. Curr Cardiol Rev. 2014;10(4):336-48.
10. Costa RR, Vieira AF, Coconcelli L, Fagundes AO, Buttelli ACK, Pereira LF, Stein R, Kruel LFM. Statin Use Improves Cardiometabolic Protection Promoted By Physical Training in an Aquatic Environment: A Randomized Clinical Trial. Arq Bras Cardiol. 2021; 117(2):270-278. doi: https://doi.org/10.36660/abc.20200197
11. Correa CV; Teixeira BC; Bittencourt A; Oliveira AR. Effects of strength training on blood lipoprotein concentrations in postmenopausal women. J Vasc Bras. 2014;13(4):312-7.

Original Article

Association between Clinical Risk Score (Heart, Grace and TIMI) and Angiographic Complexity in Acute Coronary Syndrome without ST Segment Elevation

Alexandre Vianna Cedro,[1] Diandro Marinho Mota,[1] Louis Nakayama Ohe,[1] Ari Timerman,[1] José Ribamar Costa,[1] Laura de Siqueira Castro[2]

Instituto Dante Pazzanese de Cardiologia,[1] São Paulo, SP - Brazil

Universidade Federal de São Paulo Escola Paulista de Medicina,[2] São Paulo, SP - Brazil

Abstract

Background: **GRACE, TIMI and HEART scores have been previously validated to predict serious untoward events among patients with non-ST elevation acute coronary syndrome (Non-ST ACS). However, the ability of these scores to discriminate the angiographic complexity of coronary artery disease has not been clearly established.**

Objectives: **We sought to evaluate the correlation between clinical scores (TIMI, GRACE and HEART) and the anatomical complexity assessed by SYNTAX score, among non-ST ACS patients undergoing cinecoronariography.**

Methods: **Transversal cohort encompassing patients with diagnosis of Non-ST ACS referred to invasive stratification in our single center, between July 2018 and February 2019. Association between the scores was established by the Pearson's linear correlation test while the accuracy of the clinical scores versus SYNTAX score was determined with the ROC curve.**

Results: **A total of 138 patients were enrolled. Median GRACE, TIMI and HEART scores were 97, 3 and 5, respectively, whereas the median SYNTAX was 8. There was a positive correlation between the SYNTAX and the HEART (ρ =0.29; p<0.01) and GRACE (ρ =0.18; p<0.01) scores, but the correlation with TIMI reached no statistical significance (ρ =0.15; p=0.08). The HEART score was also the one with the highest area under the curve to predict a SYNTAX ≥32 [HEART = 0.81 (IC95% 0.7-0.91). HEART> 4 presented 100% sensitivity, with 50% specificity; and GRACE> 139 showed 55% sensitivity and 97% specificity for high SYNTAX.**

Conclusion: **The clinical scores presented a positive, although modest, association with the SYNTAX score. The combined use of HEART and GRACE offers good accuracy for detecting angiographic complexity.**

Keywords: **Acute Coronary Syndrome. Organ Dysfunction Scores; Hospitalization; Thrombosis; Myocardial Infarction; Angiography/complications.**

Introduction

Non-ST elevation acute coronary syndrome (Non-ST ACS) has a broad spectrum of severity, which varies according to electrocardiographic, clinical, and laboratory characteristics. Thus, risk stratification is fundamental in every patient with Non-ST ACS and directly influences initial management. It has been shown that using multivariate models is the most accurate way to predict risk, being superior to clinical impression alone.[1,2]

The Thrombolysis in Myocardial Infarction (TIMI), Global Registry for Acute Coronary Events (GRACE), and Heart Score (HEART) are the most commonly used scores in patients with chest pain in the emergency room and have been validated to predict undesirable clinical outcomes. However, these scores are not intended to estimate the extent of coronary artery disease.[3-6]

The evaluation of anatomical complexity using the SYNTAX score is as fundamental in the definition of revascularization strategy as the analysis of clinical scores, with important prognostic implications.[7]

The SYNTAX study, which gave rise to the score, compared late clinical outcomes in patients requiring multiple grafts treated with angioplasty (PCI) and coronary artery bypass grafting (CABG). The authors found that CABG had a more favorable outcome than PCI in patients with more extensive coronary artery diseases (SYNTAX ≥ 33).[8] Thus, the determination of the SYNTAX score may also conflict with the clinical approach, supporting the decision to use dual antiplatelet therapy when the anatomy is favorable for the surgical approach.[7,8]

Despite the importance of identifying prognostic factors dependent on the extent of coronary disease, few studies

Mailing Address: Alexandre Vianna Cedro •
Instituto Dante Pazzanese de Cardiologia – Av. Dr. Dante Pazzanese, s/n. Postal Code 04012-909, São Paulo, SP – Brazil
E-mail: alexandrecedro@hotmail.com, alexandre.cedro@einstein.br
Manuscript received June 24, 2019, revised manuscript June 27, 2020, accepted August 05, 2020

DOI: https://doi.org/10.36660/abc.20190417

have investigated the correlation between clinical scores and anatomical complexity. Controversial results have been reported when the TIMI and GRACE scores have been used to analyze this relationship, and no study has associated the HEART score with the complexity of coronary artery disease.[9-11]

Therefore, this study aims to evaluate the association between TIMI, GRACE, and HEART[12] scores and the complexity of coronary artery disease revealed by coronary angiography in patients with Non-ST ACS.

Methods

Population selection

This is an observational and longitudinal study conducted at the Dante Pazzanese Institute of Cardiology (São Paulo-SP, Brazil) between July 2018 and February 2019 and approved by the research ethics committee of the institution. All patients signed an informed consent form at the time of hospitalization.

We included patients over 18 years old admitted with a diagnosis of non-ST ACS in the emergency department and who underwent coronary angiography during hospitalization. Patients with CABG, ST-segment elevation acute myocardial infarction (STEMI), or presumed new left bundle-branch block were excluded.

Clinical scores

All patients were evaluated and stratified by the HEART, TIMI, and GRACE scores at the time of hospitalization. Clinical data, admission electrocardiogram, the first creatinine dose, and the highest troponin value in the first 12 hours of care were used to calculate the scores. Patients were considered as having a high troponin level when their ultrasensitive troponin T value was ≥0.01 μg/L, that is, higher than the 99th percentile of the general population.

Criteria previously defined in validation studies were used to calculate the scores. TIMI score was calculated through the seven usual dichotomous variables. The presence of each variable added one point to the total score, which ranged from zero to seven. A TIMI score ranging from 5 to 7 was considered high.[3]

The GRACE score was calculated using eight variables and was revised using the score calculator (http://www.grace.org). A final score higher than 139 was considered high, as recommended in the main guidelines.[1,2]

The HEART score ranged from 0 to 10 according to its five usual variables (history, ECG, age, risk factors, and troponin value). After the calculation, patients with scores between 7 and 10 were classified as high risk.[5]

After conducting invasive risk stratification, all catheterizations were analyzed by an experienced interventional cardiologist. All analysis was performed by a single blind investigator, using Quantitative Coronary Analysis (QCA). The SYNTAX score was calculated and revised using the official score calculator (http://www.syntaxscore.com), checking the instructions and using the software available on the page.

Arteries with diameter ≥1.5 mm and stenosis ≥50% were evaluated. The score was defined for each patient according to the following parameters: dominance; number of lesions; presence of chronic occlusion, trifurcation, bifurcation, ostial lesion, severe tortuosity, calcification, and thrombus; and lesion length >20 mm. A narrowing of 50% of the lumen occurring 3 mm from the carina in an artery with branches of at least 1.5 mm indicated bifurcation. A radiopaque lesion observed even before the contrast injection indicated severe coronary calcification. After calculating the score, each patient was classified as having low- (≤ 22), moderate- (23-32) or high (≥ 33) SYNTAX score.[7]

Statistical analysis

Data are represented as absolute frequency with percentage for categorical variables and as mean ± standard deviation (SD) or median with interquartile interval for continuous variables for continuous variables, according to normality and distribution criteria. Cross tables and the chi-squared test were used to compare proportions between groups, and analysis of variance was used to compare means. To compare the distribution of continuous variables we used General Linear Models

The normality of distribution of continuous variables was assessed by the Kolmogorov-Smirnov test, the homogeneity of distribution between groups by the Levene test. The results of the comparison between groups were confirmed by the nonparametric Mann-Whitney test.

Sample size was not calculated, with the number of patients being determined by simple scrutiny. The association between the SYNTAX score and other risk scores—TIMI, GRACE, and HEART—was evaluated using bivariate correlations adopting the Spearman coefficient for nonparametric variables.

ROC curves were used to determine whether the TIMI, GRACE, and HEART scores could accurately identify patients with moderate- and high SYNTAX scores. Two binary variables were created, stratifying patients by low versus moderate-high SYNTAX score (≥23) and low-moderate versus high SYNTAX score (>32). Sensitivity and specificity were calculated based on the previously described cutoff points of the TIMI, GRACE, and HEART scores. P values < 0.05 indicated statistical significance. The SPSS version 25 statistical software was used for data analysis.

Results

From July 2018 to February 2019, 292 patients admitted with ACS and eligible for inclusion in the study were admitted. Of these, 105 (35.9%) individuals who did not undergo cardiac catheterization at that time, 24 (8.2%) who were diagnosed with STEMI, and 25 (8.6%) who had a history of CABG were excluded.

Table 1 shows the characteristics of the final sample. Of the 138 patients analyzed, 68.1% were male with a mean age of 60 ± 13 years, and 32.2% had NSTEMI (Table 1). The median of GRACE, TIMI, and HEART scores were 98.1 (76.5-115.7), 2.8 (2-4) e 5 (4-6), respectively. Significant coronary

Table 1 – Characteristics of the Participants at Baseline

	Total	Syntax <23	Syntax ≥23	p	Syntax ≤32	Syntax >32	p
N (%)	**138 (100)**	**114 (82.6)**	**23 (16.7)**		**126 (91.3)**	**11 (8.0)**	
Male, n (%)	94 (68.1)	77 (73.9)	17 (73.9)	0.63	86 (68.3)	8 (72.7)	1.0
Age, mean ± SD	60.2 ± 11.3	59.4±10.7	65.0±9.2	0.02	59.4±10.9	67.4±10.6	0.02
BMI, mean ± SD	27.9 ± 4.9	27.9 ± 5.1	27.9 ± 3.9	0.94	27.8 ± 4.9	28.9 ± 4.9	0.49
Obesity, n (%)	39 (28.3)	34 (30.6)	5 (21.7)	0.46	37 (30.1)	2 (18.2)	0.51
Diabetes, n (%)	50 (36.2)	41 (36.0)	9 (39.1)	0.82	44 (34.9)	6 (54.5)	0.21
Dyslipidemia, n (%)	72 (52.2)	62 (54.4)	10 (45.5)	0.49	68 (54.4)	4 (36.4)	0.35
Hypertension, n (%)	115 (83.3)	94 (82.5)	20 (87.0)	0.76	105 (83.3)	9 (81.8)	1.0
Smoking, n (%)	37 (26.8)	33 (28.9)	4 (17.4)	0.31	35 (27.8)	2 (18.2)	0.73
Sedentarism, n (%)	132 (95.7)	109 (96.5)	22 (95.7)	1.00	120 (96.0)	11 (100)	1.0
Cr, mediana (IIQ)	0.9 (0.7-1.0)	0.9(0.71-1.0)	0.8 (0.7-1.1)	0.89	0.9 (0.7-1.0)	0.8 (0.7-1.1)	0.97
Diagnosis, n(%)							
Unstable angina	93 (67.3)	80 (70.2)	13 (56.5)	0.23	89 (70.6)	4 (36.6)	0.04
NSTEMI	45(32.6)	34 (29.8)	10 (43.5)		37 (29.4)	7 (45.5)	

Statistics: Chi-square test for comparison of proportions and Generalized Linear Models (GLM) for comparison of continuous variables. BMI: body mass index; Cr: creatinine; NSTEMI: non-ST-segment acute myocardial infarction. Obesity was defined as BMI> 30 kg/m²

stenosis was not observed in 29.7% of patients, while 43.7% of patients required multiple grafts. All three clinical scores were higher in patients with moderate or high SYNTAX score than in those with low SYNTAX score (Table 2).

Figure 1 illustrates the correlation between the three clinical scores and SYNTAX. A modest correlation was observed in relation to HEART ($\rho = 0.29$; $p < 0.01$) and GRACE ($\rho = 0.18$; $p < 0.01$), however the correlation with TIMI did not reach statistical significance ($\rho = 0.15$; $p = 0.08$) .

When evaluating the ROC curve, we observed that raised levels of all clinical scores could accurately predict a high SYNTAX score (>32). The association of SYNTAX score with HEART, TIMI, and GRACE scores resulted in an area under the receiver operating characteristic ROC curve (AUC) of 0.81 (95% CI 0.7-0.91, $p < 0.01$), 0.79 (95% CI 0.64-0.97), and 0.76 (95% CI 0.53-0.79), respectively. (Figure 2)

HEART greater than 5 showed 64% sensitivity and 70% specificity to evaluate high SYNTAX (>32). When greater than 4, it presented 100% sensitivity, with 50% specificity.

GRACE greater than 102 gave 82% sensitivity and 65% specificity. At the original cutoff point> 139 gives 55% sensitivity but 97% specificity. Thus, using both scores (GRACE and HEART), a more accurate assessment was possible to predict anatomical complexity.

Due to the low number of endpoints and a short follow-up period, there was not enough statistical power to investigate the relationship between clinical scores and outcomes such as mortality and reinfarction. There was 1 case of death (0.72%) and 1 case of reinfarction (0.72%), with patients having SYNTAX of 33 and 19, respectively, and the GRACE, TIMI and HEART scores of 69, 5 and 5 in the first and 126, 1 and 5 in the second.

Discussion

The present study evaluated the three most relevant clinical scores used in the context of Non-ST ACS. The GRACE and TIMI scores have been extensively studied and validated in several populations due to their ability to predict unfavorable clinical events, being recommended by the main international guidelines.[1,2]

The HEART score has been increasingly used in patients with acute chest pain in the emergency room due to its high negative predictive value and ability to reduce unnecessary hospitalizations. However, high values of HEART score are known to predict unfavorable events so that it is worth investigating whether HEART score is associated with anatomical complexity.[6,13]

The determination of the extent of coronary artery disease, through the identification of clinical prognostic factors, plays an important role in the definition of the best revascularization strategy and ideal drug therapy. Thus, the SYNTAX score was used to quantify the extent of coronary disease.

Some studies have already evaluated the association between TIMI and GRACE scores with the number of affected arteries. Mahmood et al. found that TIMI > 4 or GRACE > 133 are associated with a higher probability of the patient requiring multiple grafts or having significant stenosis in the left main coronary artery ($p < 0.05$). Bakler et al. evaluated the association of clinical score with anatomical complexity using the SYNTAX score. A positive linear association between SYNTAX score and GRACE score was observed, with a ratio coefficient of $r = 0.43$ ($p < 0.01$) and AUC of 0.65 (CI 95% 0.56-0.74; $p < 0.001$). TIMI score was not associated with SYNTAX score ($r = 0.121$, $p = 0.121$), and HEART score was not evaluated. It should be noted that patients with STEMI (46% of the sample) were included, and these patients are not usually evaluated using the GRACE score.[14]

Table 2 – Diagnosis and hospital outcomes

	Total	SYNTAX < 23	SYNTAX ≥ 23	p	SYNTAX ≤ 32	SYNTAX > 32	p
N (%)	**138 (100)**	**114 (82.6)**	**23 (16.7)**		**126 (91.3)**	**11 (8)**	
Days of hosp. ± SD							
Median (IIQ)	3 (2-6)	3 (2-5)	8 (3-20)	< 0.001	3 (2-5)	14 (7-23)	< 0.001
Access, n (%)							
Radial	97 (70.3)	82 (71.9)	14 (60.9)	0.32	90 (71.4)	6 (54.5)	0.30
Femoral	41 (29.7)	32 (28.1)	9 (39.1)		36 (28.6)	5 (45.5)	
Access, n (%)							
Without CAD	41 (29.7)	41 (36.0)	0		41 (32.5)	0	
One artery	42 (30.4)	42 (36.8)	0	< 0.001	42 (33.3)	0	< 0.001
Two arteries	20 (14.6)	18 (15.8)	2 (8.7)		18 (14.3)	2 (18.2)	
Three arteries	34 (39.1)	13 (11.4)	21 (91.3)		25 (19.9)	9 (81.8)	
LMCA, n (%)	13 (9.4)	7 (6.1)	6 (26.1)	0.001	8 (6.3)	5 (45.5)	0.001
GRACE							
Median (IIQ)	97 (77-115)	93 (75-112)	105 (92-140)	0.020	94 (75-112)	140 (103-175)	< 0.001
>139, n(%)	9 (6.5)	2 (1.8)	7 (31.8)	< 0.001	3 (2.4)	6 (54.5)	< 0.001
ASC			0.66 (0.53-0.79)			0.76 (0.53-0.79)	
TIMI							
Median (IIQ)	3 (2-4)	3 (2-3)	3 (2-5)	0.024	3 (2-3)	5 (3-6)	0.004
≥5. n(%)	16 (11.6)	9 (7.9)	7 (30.4)	0.006	10 (54.4)	6 (54.5)	< 0.001
ASC			0.66 (0.53-0.79)			0.81 (0.64-0.97)	
HEART							
Median (IIQ)	5 (4-6)	4 (4-6)	6 (5-8)	< 0.001	5 (4-6)	7 (5-8)	0.001
≥7 n (%)	26 (18.8)	18 (15.8)	8 (34.8)	0.044	20 (15.9)	6 (54.5)	0.006
ASC			0.72 (0.62-0.83)			0.81 (0.70-0.92)	
SYNTAX							
Median (IIQ)	8 (0-17)	6 (0-12)	32 (26-34)	< 0.001	7 (0-14)	34 (33-35)	0.001

Statistics: Chi-square test for comparison of proportions and Generalized Linear Models (GLM) for comparison of continuous variables. ASC: Area Under the ROC Curve; LMCA: Left Main Coronary Artery.

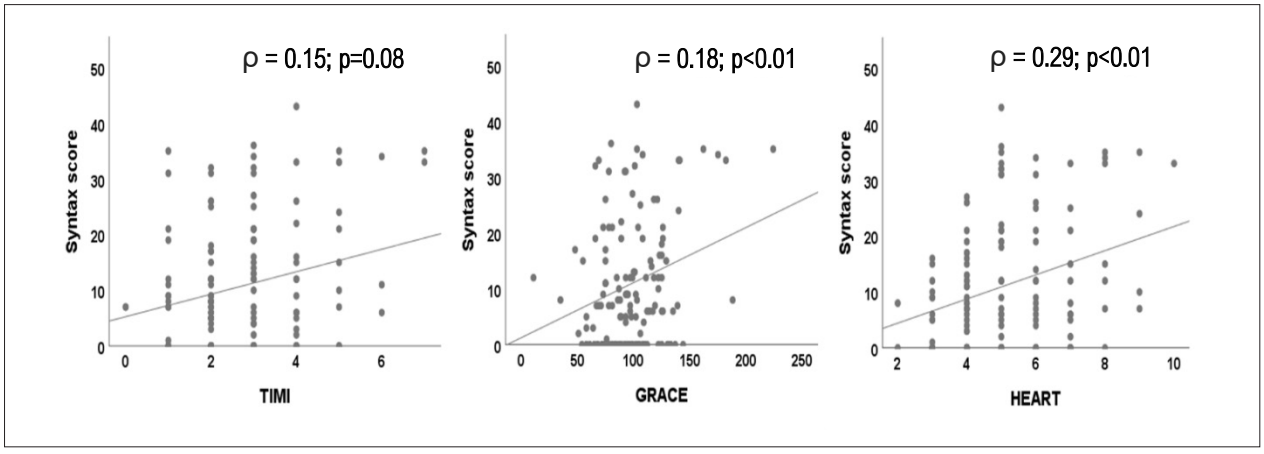


Figure 1 – *Scatter plots between the numerical values of the SYNTAX scores vs. TIMI, GRACE, and HEART scores. Note: (ρ) Spearman's rho coefficient.*

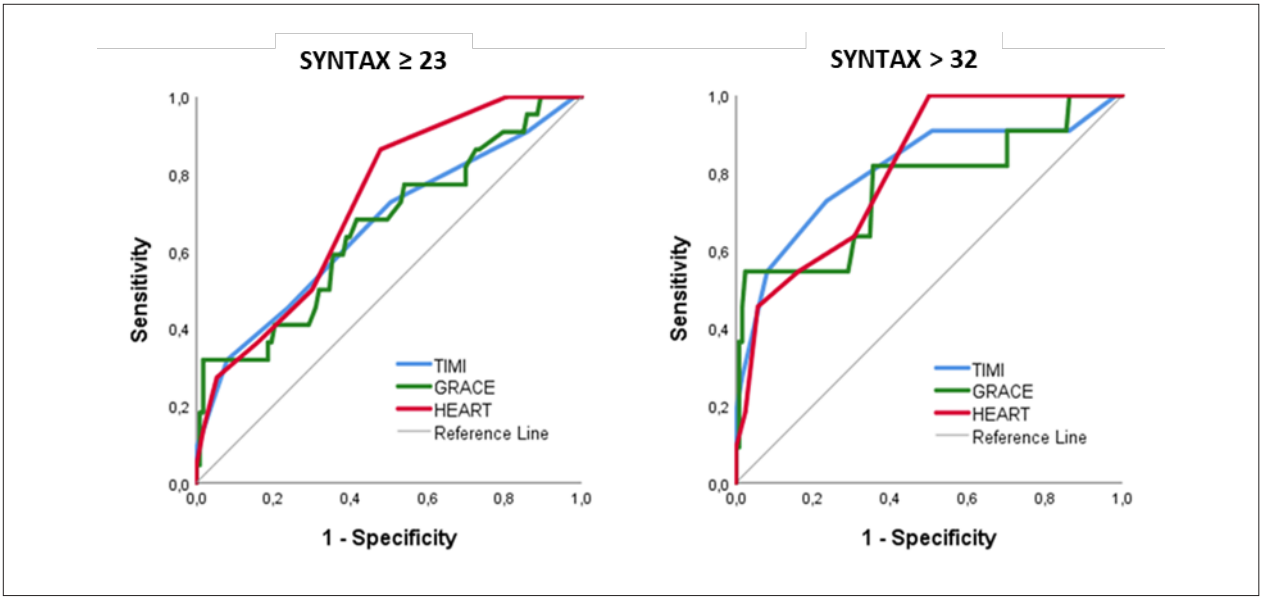


Figure 2 – *ROC curves for detecting moderate or high SYNTAX scores, according to TIMI, GRACE, and HEART scores. A – GRACE score with AUC of 0.66 (95% CI 0.53-0.79, p < 0.01); TIMI score of 0.66 (95% CI 0.53-0.79); HEART score of 0.72 (95% CI 0.62-0.83), p < 0.01. B – GRACE score with AUC of 0.76 (95% CI 0.53-0.79); TIMI score of 0.79 (95% CI 0.64-0.97); HEART score of 0.81 (95% CI 0.70-0.91), p < 0.01.*

Hammami et al.[15] retrospectively evaluated the GRACE and TIMI scores of 238 patients and observed that both scores showed positive correlation with the SYNTAX score. A Pearson correlation coefficient of r = 0.23 (p < 0.001) was found between SYNTAX score and GRACE score and a Pearson correlation coefficient of r = 0.2 (p = 0.002) was found between the SYNTAX score and the TIMI score. These values were similar to those observed in Figure 1, which showed a slightly higher correlation when comparing the GRACE (r = 0.26; p < 0.01) and the TIMI (r = 0.24; p < 0.01) scores. It should be noted that we only considered lesions > 70% when calculating the SYNTAX score. Although plausible, this form of analysis is not validated by official calculators or studies that investigate the accuracy of the score or the prognosis of patients.[15] In a recent study, Silvano et al.[16] evaluated 183 patients, including patients with STEMI (29.5%), and observed a positive but low correlation between GRACE and SYNTAX scores (r = 0.2, p = 0.005). TIMI and HEART scores were not evaluated.[16]

Some of the studies evaluating the association between risk scores and anatomical complexity reported a linear correlation between GRACE and SYNTAX scores, with controversial results when TIMI score was used, similar to the result observed in the present study.

This is the first study to do combined analysis of GRACE and HEART, demonstrating the significant increase in accuracy in predicting angiographic complexity when using both clinical scores simultaneously.

In this study, when the HEART score was greater than 4, the sensitivity was 100%, with a specificity of 50%; and when GRACE greater than 139 the sensitivity is 55% and specificity is 97% for high SYNTAX. Therefore, this study hypothesizes that, in specific scenarios of high clinical risk scores (GRACE> 139 and HEART> 4), the team and the patient can prepare for a surgical approach, due to the higher probability of high SYNTAX, by elevated SYNTAX.

One of the noteworthy limitations of this study is the small number of patients for a study conducted in a single center, as well as the absence of a second evaluator to analyze the methods and the other scores.

Conclusion

The clinical scores presented a positive, although modest, association with the SYNTAX score. The combined use of HEART and GRACE, offers good accuracy for detecting angiographic complexity.

Author Contributions

Conception and design of the research and Acquisition of data: Cedro AV, Mota DM, Ohe LN; Analysis and interpretation of the data: Cedro AV, Mota DM, Castro LS; Statistical analysis: Cedro AV, Castro LS; Writing of the manuscript: Cedro AV; Critical revision of the manuscript for intellectual contente: Mota DM, Ohe LN, Timerman A, Costa JR, Castro LS.

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. 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 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.
2. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. ACC/AHA Task Force Members. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. 2014; 130(25): e344-426.
3. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. Jama. 2000; 284(7): 835-42.
4. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP et al. Global registry of acute coronary events investigators. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med. 2003; 163(19): 2.345-53.
5. Backus BE, Six AJ, Kelder JC, Bosschaert MAR, Mast EG, Mosterd A et al. A prospective validation of the HEART score for chest pain patients at the emergency department. Int J Cardiol. 2013; 168(3): 2.153-8.
6. Poldervaart JM, Langedij M, Backus B, Dekker IMC, Six AJ, Doevendans PA et al. Comparison of the GRACE, HEART and TIMI score to predict major adverse cardiac events in chest pain patients at the emergency department. Int J Cardiol. 2017; 227: 656-61.
7. Neumann F, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019; 40(2): 87-165.
8. Sianos G, Morel MA, Kappetein AP, Morice MC, Colombo A, Dawkins K et al. The SYNTAX score: an angiographic tool grading the complexity of coronary artery disease. EuroIntervention. 2005; 1(2): 219-27.
9. Cakar MA, Sahinkus S, Aydin E, Vatan MB, Keser N, Akdemir R et al. Relation between the GRACE score and severity of atherosclerosis in acute coronary syndrome. J Cardiol. 2014; 63(1): 24-8.
10. Garcia S, Canoniero M, Peter A, Marchena A, Ferreira A. Correlation of TIMI riskscore with angiographic severity and extent of coronary arterydisease in patients with non-ST-elevation acute coronary syndromes. Am J Cardiol. 2004; 93(7): 813-6.
11. Ben Salem H, Ouali S, Hammas S, Bougmiza I, Gribaa R, Ghannem K et al. Correlation of TIMI risk score with angiographic extent and severity of coronary artery disease in non-ST-elevation acute coronary syndromes. Ann Cardiol Angeiol (Paris). 2011; 60(2): 87-91.
12. Mahmood M, Achakzai AS, Akhtar P, Zaman KS et al. Comparison of the TIMI and the GRACE risk scores with the extent of coronary artery disease in patients with non-ST-elevation acute coronary syndrome. J Pak Med Assoc. 2013; 63(6): 691-5.
13. Poldervaart JM, Reitsma JB, Backus BE, Koffijberg H, Veldkamp RF, Haaf ME et al. Effect of using the HEART score in patients with chest pain in the emergency department: a stepped-wedge, cluster randomized trial. Ann Intern. 2017; 166(10): 689-97.
14. Bekler A, Altun B, Gazi E, Temiz A, Barutçu A, Güngör Ö et al. Comparison of the GRACE risk score and the TIMI risk index in predicting the extent and severity of coronary artery disease in patients with acute coronary syndrome. Anatol J Cardiol. 2015; 15(10): 801-6.
15. Hammami R, Jdidi J, Mroua J, Kallel R, Hentati M, Abid L et al. Accuracy of the TIMI and GRACE scores in predicting coronary disease in patients with non-ST-elevation acute coronary syndrome. Rev Port Cardiol. 2018; 37(1): 41-9.
16. Silvano GP, Silva LS, Faria EC, Trevisol DJ. The GRACE score is not a good predictor of angiographic complexity in acute coronary syndrome. J Transcat Intervent. 2019; 27:1-6.

NSTE-ACS at the Emergency: Can You Guess What is Under the Umbrella?

Bruno Rocha[1,2] *and Carlos Aguiar*[1,2]

Departamento de Cardiologia, Hospital de Santa Cruz, Centro Hospitalar Lisboa Ocidental,[1] *Lisboa - Portugal*

Unidade de Insuficiência Cardíaca Avançada e Transplante Cardíaco, Hospital de Santa Cruz, Centro Hospitalar Lisboa Ocidental,[2] *Lisboa - Portugal*

Short Editorial related to the article: Association between Clinical Risk Score (Heart, Grace and TIMI) and Angiographic Complexity in Acute Coronary Syndrome without ST Segment Elevation

The reasoning behind the often-difficult task of deciding whether, when and how to treat the patient with established Cardiovascular Disease (CVD) might be based on two simple questions: (1) Are we treating an acute event?, and (2) What is my patient at risk of in the future? Whilst the first question implies an expedite straightforward treatment, the second premise depends mostly on risk stratification and, thus, the capability of one to anticipate the likelihood of an event.[1] Withal, the physician often encounters a scenario in which the two questions must be addressed altogether. Accordingly, the response is more likely one of a probability rather than a categorical (yes or no) answer. This is the outline in umbrella diagnoses, as is non-ST segment elevation (NSTE) Acute Coronary Syndromes (ACS).[2,3]

There are a multitude of clinical tools in Cardiovascular Medicine[4–6] that aid physicians in the decision-making process, often surpassing the "educated guess" in acute settings.[7,8] However, the use of these tools in NSTE-ACS is particularly challenging for a number of reasons:

Firstly, is this really NSTE-ACS? The diagnosis requires the combination of a cardiac biomarker variation over time with either myocardial ischemic symptoms or new ischemic ECG findings, or imaging of loss of viable myocardium or new regional wall motion abnormality with an ischemic pattern.[1] Importantly, high-sensitivity cardiac troponins have facilitated the identification of NSTE Myocardial Infarction [particularly by reducing the likelihood of a missed "unstable angina" (UA) with previous biomarkers] but have somewhat complicated its differential diagnosis – stressing the scenario in which one must consider the more-inclusive myocardial injury term.[1,9] Furthermore, symptoms and ECG changes might be attributable to non-ischemic mechanisms, thus translating into their mediocre specificity.[9,10]

Secondly, how severe is the underlying disease causing NSTE-ACS? Even when considering type-1 (spontaneous, atherosclerosis-related) Myocardial Infarction,[9] the spectrum of coronary artery disease (CAD) may consist of single-vessel and/or distal stenosis vs. more complex severe proximal and/or three-vessel disease. The plot further thickens if one considers additional pathophysiological mechanisms that can be at work[11] – the so-called type-2 Myocardial Infarction.[9] In these cases, notably, CAD might be present merely as a confounding bystander.

Finally, how should I treat this patient with NSTE-ACS? The decision should be based on clinical characteristics and CAD severity. It may involve a conservative approach or myocardial revascularization,[1] by means of a percutaneous coronary intervention and/or coronary artery bypass grafting (CABG). However, the latter has not been incorporated into score systems but surely influences prognosis.[12,13]

Cedro et al. present an article where clinical scores (TIMI, GRACE and HEART) were used to predict the complexity of the underlying CAD, as per the SYNTAX score. To do so, the authors designed an observational study enrolling 138 patients with NSTE-ACS (with a mean age of 60 ± 11 years, of whom 68% were males, and often presenting with traditional cardiovascular risk factors). Most had UA (67,3%) and the spectrum of CAD severity was broad, as one may infer from the inclusion of patients with multi-vessel disease (53,7%) or absence of significant (>50%) coronary stenosis (29,7%). The authors have found that the correlations between the clinical and SYNTAX scores were moderate at best. Nonetheless, the HEART score performed particularly well in predicting complex CAD (i.e., SYNTAX >32, with an area under the curve of 0.81). Interestingly, a cut-off value of >4 and ≥140 for HEART and GRACE scores yielded a sensitivity and specificity of 100% and 97%, respectively, to predict such severe CAD.[14]

Given the abovementioned results, it is proposed that the combined use of the HEART and GRACE scores might be useful in detecting complex CAD.[14] It should be noted, however, that this is a small exploratory single-center study, mostly including patients with UA (in whom the GRACE score has not been extensively validated, as far as prognosis is concerned). Nonetheless, it would be an alluring hypothesis to investigate whether these scores might be incorporated as a valid tool in the pathway of care of NSTE-ACS patients, namely: (1) Could these be used as a novel criterion for immediate invasive strategy listing?, and (2) Could these differentiate between patients in whom P2Y12 pre-treatment strategy is safe and desirable from those in whom it might cause harm (e.g. potentially delaying CABG)?

In conclusion, the preliminary findings of this study suggest an interesting concept: rather than using the usual clinical tools

Keywords

Acute Coronary Syndrome; Non-ST Elevated Myocardial Infarction; Biomarkers; Myocardial Ischemia; Troponin; Electrocardiography/methods.

Mailing Address: Carlos Aguiar •
Departamento de Cardiologia, Hospital de Santa Cruz - Avenida Professor Dr. Reinaldo dos Santos, Postal Code 2790-134 Carnaxide, Lisboa - Portugal
E-mail: ctaguiar@gmail.com

DOI: https://doi.org/10.36660/abc.20210516

to predict the risk of outcomes, we might want to use them to determine whether there might be a severe complex condition underlying CAD, warranting surgical revascularization.[15] Whether these multivariate risk prediction model tools might improve outcomes remains unclear, yet this hypothesis is worth being prospectively investigated. The presented work adds a small but important piece supporting this rationale, unveiling what might be truly under the umbrella.

References

1. Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL, et al. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST elevation The 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. 2021 Apr 7;42(14):1289-367.
2. George B, Misumida N, Ziada KM, George B. Revascularization Strategies for Non-ST-Elevation Myocardial Infarction. Curr Cardiol Rep. 2019 Apr 10;21(5):39.
3. Feldman L, Steg PG, Amsallem M, Puymirat E, Sorbets E, ElbazM, et al. Medically managed patients with non – ST-elevation acute myocardial infarction have heterogeneous outcomes, based on performance of angiography and extent of coronary artery disease. Eur Heart J Acute Cardiovasc Care. 2017;6(3):262-71.
4. Ascenzo F, Biondi-Zoccai G, Moretti C, Boliati M, Ameda P, Sciuto F, et al. TIMI, GRACE and alternative risk scores in Acute Coronary Syndromes : A meta-analysis of 40 derivation studies on 216 , 552 patients and of 42 validation studies on 31 , 625 patients. Contemp Clin Trials. 2012 May;33(3):507-14.
5. Cortés M, Haseeb S, Lambardi F,Arbucci R, Ariznovarreta P, Resi S, et al. The HEART score in the era of the European Society of Cardiology 0 / 1-hour algorithm. Eur Heart J Acute Cardiovasc Care. 2020 Feb;9(1):30-8.
6. Torralba F, Navarro A, Hoz JC,la Hoz JC, Ortiz C, Botero A, et al. HEART, TIMI, and GRACE Scores for Prediction of 30-Day Major Adverse Cardiovascular Events in the Era of High-Sensitivity Troponin. Arq Bras Cardiol. 2020 Mar 13;114(5):795-802.
7. Fanaroff AC, Rymer JA, Goldstei, SA, Simel DL. Does This Patient With Chest Pain Have Acute Coronary Syndrome ? The Rational Clinical Examination Systematic Review. JAMA. 2015 Nov 10;314(18):1955-65.
8. Oliver G, Reynard C, Morris N, Body R. Can Emergency Physician Gestalt " Rule In " or " Rule Out " Acute Coronary Syndrome : Validation in a Multicenter Prospective Diagnostic Cohort Study. Acad Emerg Med. 2020 Jan;27(1):24-30.
9. Thygesen T, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction Eur Heart J. 2019;40(3):237-69.
10. Carlton EW, Pickering JW, Greenslade J, Cullen L, Than M, Kendall J, et al. Assessment of the 2016 National Institute for Health and Care Excellence high-sensitivity troponin rule-out strategy. Heart. 2018 Apr; 104(8): 665–72.
11. Safdar B, Spatz E, Dreyer RP, Beltrame JF, Lichtman JH, Spertus JA, et al. Presentation, Clinical Profile, and Prognosis of Young Patients With Myocardial Infarction With Nonobstructive Coronary Arteries (MINOCA): Results From the VIRGO Study. (2018). J Am Heart Assoc. 2018;7(13):e009174.
12. Smilowitz NR, Mahajan AM, Roe MT, Helikamp AS, Criswell K, Gulati M, et al. Mortality of Myocardial Infarction by Sex , Age , and Obstructive Coronary Artery Disease Status in the ACTION Registry – GWTG (Acute Coronary Treatment and Intervention Outcomes Network Registry – Get With the Guidelines). Circ Cardiovasc Qual Outcomes. 2017 Dec;10(12):e003443.
13. Menozzi A, Servi S, Rossini R, Ferlini M, Lina D, Abrignani MG, et al. Patients with non-ST segment elevation acute coronary syndromes managed without coronary revascularization : A population needing treatment improvement. Int J Cardiol. 2017 245:35-42.
14. Cedro AV, Mota DM, Ohe LN, Timerman A, Costa JR, Castro LS. Association between Clinical Risk Score (Heart, Grace and TIMI) and Angiographic Complexity in Acute Coronary Syndrome without ST Segment Elevation. Arq Bras Cardiol. 2021; 117(2):281-287. doi: https://doi.org/10.36660/abc.20190417
15. Yildirim A, Kucukosmanoglu M, Yavuz F, Koyunsever NY, Cekici Y, Dogdus M, et al. Comparison of the ATRIA , CHA2DS2-VASc , and Modified Scores ATRIA-HSV, CHA2DS2-VASc-HS, for the Prediction of Coronary Artery Disease Severity. Angiology. 2021;Feb 08;3319721991410.

Naringin and Trimetazidine Improve Baroreflex Sensitivity and Nucleus Tractus Solitarius Electrical Activity in Renal Ischemia-Reperfusion Injury

Negin Amini,[1,2] Alireza Sarkaki,[1,2] Mahin Dianat,[1,2] Seyyed Ali Mard,[1,2] Akram Ahangarpour,[1,2] Mohammad Badavi[1,2]

Department of Physiology, School of Medicine, Ahvaz Jundishapur University of Medical Sciences,[1] Ahvaz - Iran

The Persian Gulf Physiology Research Center, Research Institute of Basic Medical Sciences, Ahvaz Jundishapur University of Medical Sciences,[2] Ahvaz - Iran

Abstract

Background: **Nucleus tractus solitarius (NTS) is a brain area that plays a key role in kidney and cardiovascular regulation via baroreceptors impulses.**

Objectives: **The aim of this study was to evaluate the effect of naringin (NAR) and trimetazidine (TMZ) alone and their combination on NTS electrical activity and baroreceptor sensitivity (BRS) in renal ischemia- reperfusion (I/R) injury.**

Methods: **Forty male Sprague-Dawley rats (200- 250 g) were allocated into 5 groups with 8 in each. 1) Sham; 2) I/R; 3) TMZ 5 mg/kg; 4) NAR 100 mg/kg; and 5) TMZ5+ NAR100. The left femoral vein was cannulated to infuse saline solution or drug and the BRS was evaluated. I/R was induced by occlusion of renal pedicles for 45 min, followed by 4 hours of reperfusion. The NTS local electroencephalogram (EEG) was recorded before, during ischemia and throughout the reperfusion. Phenylephrine was injected intravenously to evaluate BRS at the end of reperfusion time. The data were analyzed by two-way repeated measurement ANOVA followed by Tukey's post hoc test. A p-value <0.05 was considered significant.**

Results: **NTS electrical waves did not change during ischemia time, while they significantly decreased during the entire reperfusion time. NTS electrical activity and BRS dramatically reduced in rats with I/R injury; however, administration of NAR, TMZ alone or their combination significantly improved these changes in rats with I/R injury.**

Conclusions: **The results showed that I/R injury leads to reduced BRS and NTS electrical activity and there may be an association between I/R and decreased BRS. In addition, NAR and TMZ are promising agents to treat I/R complications.**

Keywords: **Renal ischemia-reperfusion injury; Baroreflex sensitivity; Nucleus tractus solitaries; Naringin; Trimetazidine.**

Introduction

Acute kidney injury (AKI) is a major clinical problem with high prevalence that affects more than 50% of patients in the intensive care unit (ICU) and causes mortality > 60%.[1,2] Renal ischemia/reperfusion (I/R) is one of the most important causes of AKI and the generation of reactive oxygen species (ROS) play an important role in I/R injury events.[3]

The overproduction of free radicals in the I/R injury induces apoptosis and, ultimately, cell death and organ dysfunction.[3] Oxidative stress (reactive oxygen species over the antioxidant defense system) is known as a factor in I/R injury.[3] Free oxygen radicals and ROS are transmitted through the bloodstream to distant organs and are considered as intermediate agents of damage to distant organs resulting from I/R.[4,5]

The Nucleus tractus solitarius (NTS) acts as the gateway to the central nervous system for sensory information entry, which plays an important role in cardiovascular regulation.[6] Peripheral baroreceptors, chemoreceptors and renal sympathetic afferent nerves create the primary synapse in the NTS.[7] Baroreceptor dysfunction leads to loss of regulation of blood pressure fluctuations and impaired baroreceptor reflex sensitivity (BRS), which is a well-known pathophysiological basis of cardiovascular disturbances.[8] Available evidence indicates that NTS degradation leads to blood pressure alternations.[7] Therefore, NTS is one of the main centers for BRS regulation.[8]

Naringin (4, 5, 7-trihydroxyflavanone-7-rhamnoglucoside, NAR) is a polyphenol compound, which is found mainly in grapefruit and a number of citrus plants. Antimicrobial, anti-mutagenic, anticancer, anti-inflammatory, free radical scavenging and antioxidant effects of NAR have been

Mailig Address: Mohammad Badavi •
Ahvaz Jundishapur Univ Med Sci – Physiology - Dept. of Physiology, Faculty of Medicine Ahvaz Jundishapur University of Medical Sciences Ahvaz Khuzestan 6135733118 - Iran
E-mail: badavim@yahoo.com
Manuscript received February 14, 2020, revised manuscript June 17, 2020, accepted August 12, 2020

DOI: https://doi.org/10.36660/abc.20200121

shown.[9,10] The protective effects of NAR through the increased activity of antioxidant enzymes have been documented.[9,10]

Trimetazidine (1-[2, 3, 4-trimethoxybenzyl] piperazine dihydrochloride, TMZ) is an anti-ischemic drug used in unstable angina.[11] The mitochondrial permeability transition pore (mPTP), located on the inner membrane of mitochondria plays a powerful role in the production of ROS and the onset of apoptosis following I/R injury.[12] An experimental study documented that TMZ was able to inhibit mPTP and reduce the infarction size in myocardial I/R injury and caspase-3 activity.[13] Moreover, the inhibition of lipid peroxidation by TMZ has been reported.[14] The aim of this study was to evaluate the effect of NAR and TMZ alone and as a combined therapy on the local field electrical activity of the NTS at the local electroencephalography (EEG) and BRS sensitivity following renal I/R injury.

Methods

Drugs

TMZ, NAR, ketamine, xylazine and urethane were purchased from Sigma Co. USA. NAR and TMZ were dissolved in distilled water and urethane was dissolved in normal saline solution just before use.

Animals

In current study, and according to our previous study and other similar ones, forty male Sprague-Dawley rats (weighing 200- 250 g) were purchased from an animal breeding and care center of Ahvaz Jundishapur University of Medical Sciences (AJUMS). All animals were housed in standard cages (4 in each cage) under controlled temperature (22 ± 2 °C), humidity (50-55%) and a 12-h light/dark cycle (lights on at 07:00 am), with free access to food chow pellets and tap water. The rats were simply and non-randomly allocated into five groups of eight animals in each. Groups: 1) Sham, 2) I/R, 3) TMZ 5 mg/kg; I/R rats received TMZ (5 mg/kg, iv) five minutes before reperfusion,[15] 4) NAR 100 mg/kg; I/R rats received NAR (100 mg/kg, i.p) once daily for seven days before I/R,[10] and 5) TMZ 5 mg/kg + NAR 100 mg/kg; I/R rats received TMZ 5 mg/kg + NAR 100 mg/kg. Rats in sham and I/R groups received vehicle (sterile saline solution). Rats in the sham group were submitted to the same surgical procedure as the other groups, without the use of clamps and I/R induction.

Stereotaxic surgery to implant electrode

A week prior to EEG recording, the rats were anesthetized with ketamine (50 mg/kg) and xylazine (5 mg/kg), intraperitoneally. The rats' body temperature was maintained at 36.5±0.5 °C using heating pads, with their heads mounted in a stereotaxic device (Narishige Co. Japan) for electrode implantation surgery. A coated stainless steel Teflon bipolar metal wire electrode (0.005" bare, 0.008" coated, A-M systems, Inc. WA) was implanted in the NTS with Paxinos and Watson stereotaxic atlas, with coordination of AP=-14.04 mm from bregma; ML= 0.4 mm, and DV=8 mm from the dura, correspondingly.[16] All implants were fixed to the skull using dental acrylic cement and two small glass anchor bolts.

Induction of renal ischemia/reperfusion (I/R)

Rats were kept in fasting condition overnight prior to the surgery (for at least 10 h) but had free access to water. At the day of surgery, the rats from each group were anaesthetized with urethane (1.7 g/kg, i.p).[17] Then, the rats were placed on heating pads (Harvard Apparatus, UK) to keep the body temperature approximately at 37 °C. Fifteen minutes after the anesthesia, the left femoral vein was catheterized using a polyethylene catheter (PE50) to infuse saline solution or TMZ and the left femoral artery was used to measure blood pressure and baroreflex sensitivity. The left and right kidneys were exposed through a midline incision. Bilateral ischemia was induced by occluding both renal pedicles using non-traumatic clamps for 45 min. After that, the clamps were removed and reperfusion continued for 4 hours.[18]

Local EEG recording

The local field potentials (local EEG) from the rats' NTS were fed to a ML135 bio amplifier (4-Channels data acquisition Power Lab. and Lab Chart software version 7, AD Instruments Co., Australia) with 1 mV amplification, 400 Hz sampling rate, and 0.3–70 Hz band pass filtration for 5 minutes. The basic 5-sec EEG variation period were compared in all groups. The electrical power of frequency bands were measured as mV^2/Hz. The local EEG recording was performed before ischemia for 45 min, during ischemia and reperfusion time, correspondingly.

Mean arterial pressure measurement

The mean arterial pressure was recorded through the catheterization of the left femoral artery that connected to a pressure transducer and monitored by a Power Lab System (AD Instruments, Australia), before ischemia for 20 min for adaptation, during ischemia and reperfusion time.

Baroreflex sensitivity

In all groups, at the end of reperfusion period, intravenous injections of phenylephrine (10 to 20 μg/kg) were performed and the changes in blood pressure and heart rate were recorded using pressure transducer and monitored and recorded on PC, using Lab Chart software. There were 15 minute-intervals for recovery between drug injections to reach the previous level of blood pressure. For each injection, the maximum amplitude of the resulting pressure and bradycardia were used to calculate the mean arterial pressure (ΔMAP) and heart rate changes (ΔHR). The ratio of ΔHR change to ΔMAP change was used as the BRS index.[19]

Statistical analysis

The data obtained for mean arterial pressure, heart rate and local EEG were analyzed with two-way repeated measurement ANOVA followed by Tukey's test as a post hoc test for multiple comparisons using Prism software, version 6.0 (San Diego, CA). The data were expressed as the mean and standard deviation (SD). P-values < 0.05 were considered as significant differences.

Results

The effect of NAR, TMZ or their combination on NTS local field electrical activity

There were no significant alterations in NTS electrical power during pre-I/R and 45-minute ischemia period. However, NTS electrical power was dramatically decreased during the entire 1st, 2nd, 3rd and 4th hours of reperfusion period in the I/R group compared with sham rats. On the other hand, the administration of NAR and TMZ alone or in combination improved its power compared with the I/R group (Table 1).

Effect of NAR and TMZ on heart rate and arterial pressure

Renal I/R injury significantly reduced the heart rate, while pretreatment with NAR, TMZ or their combination somewhat restored the heart rate to the normal values (Figure 1). Regarding the mean arterial pressure, the results showed no differences between the different groups (Figure 2).

Effect of NAR and TMZ on BRS

As shown in figure 3, BRS was significantly reduced in the I/R injury group when compared to the sham group. However, the administration of NAR or TMZ restored it; so there was no difference between the sham, NAR and TMZ groups; however, their combination increased the BRS more significantly.

Discussion

The findings of the current study demonstrated that the I/R injury weakened NTS electrical activity and BRS. However, changes in brain waves after I/R showed that NTS electrical activity was suppressed and these changes were affected by possible heart and kidney dysfunction. Subsequent abnormal NTS electrical activity can further impair cardiac function and aggravate ischemic complications in renal function. On the other hand, pre-treatment with NAR and TMZ alone restored gamma and delta electrical powers, while its combination with TMZ improved all other NTS recorded electrical waves and also restored BRS. The afferent inputs of baroreceptors are primarily received in the NTS, which has a neuronal complex relationship with other areas of the central nervous system and the vasomotor area (the ambiguous core and rostral ventrolateral medulla).[20] Various studies have shown that diseases such as diabetes, hypertension, and renal failure mediated by oxidative stress can weaken the BRS.[21] Acute kidney injury (AKI) increases the production of anti-inflammatory cytokines, and reduces the clearance of cytokines, thus leading to increased systemic inflammatory responses.[22,23(19, 20)] A previous study has shown a relative correlation between baroreceptor dysfunction and oxidative stress.[24] Other studies showed that antioxidants can improve BRS in various experimental models.[25] On the other hand, it was found that the administration of free radical scavengers, such as superoxide dismutase (SOD) and catalase (CAT) in rabbits suffering from atherosclerosis was able to improve baroreceptor function, indicating the inhibition of ROS effect on the baroreceptor performance.[26]

In the present study, NAR and TMZ alone or in combination improved baroreceptor sensitivity, which may have occurred due to their antioxidant effects through lipid peroxidation scavenging. Our previous study has shown that NAR, TMZ or their combination can reduce glomerular dysfunction by enhancing antioxidant capacity and reducing the microRNA-10a level.[27] In line with this study and other previous findings, BRS is attenuated by oxidative stress, and polyphenol compounds improve it by scavenging free radicals.[28] In addition, extensive evidence indicated that I/R led to the reduction of nitric oxide synthesis, which is a major contributor of endothelial dysfunction, followed by baroreceptor dysfunction.[29] In this regard, NAR improves endothelial dysfunction by synthesizing and increasing nitric oxide bioavailability.[30] In a human study, it has also been shown that TMZ improved endothelial dysfunction in chronic heart failure by reducing lipid peroxidation levels.[31] An experimental study showed that TMZ reduced malondialdehyde, a renal oxidative injury index in a renal I/R injury model.[14] TMZ stimulates glucose oxidation by reducing the oxidation of

Table 1 – Effect of Naringin (NAR), Trimetazidine (TMZ) or their combination pretreatment on NTS electrical activity following renal I/R injury

Groups	EEG Power (mV2/Hz)					
	Pre-IR	Ischemia	Reperfusion Time (h)			
			1st	2nd	3rd	4th
Sham	0.723 ± 0.117	0.675 ± 0.126	0.699 ± 0.116	0.68 ± 0.104	0.673 ± 0.104	0.695 ± 0.13
IR	0.725 ± 0.081	0.652 ± 0.052	0.635 ± 0.095***	0.61 ± 0.082***	0.587 ± 0.042***	0.592 ± 0.025***
NAR	0.705 ± 0.034	0.653 ± 0.051	0.673 ± 0.029	0.65 ± 0.033#	0.63 ± 0.041#	0.646 ± 0.038##
TMZ	0.712 ± 0.067	0.668 ± 0.085	0.673 ± 0.073	0.65 ± 0.069#	0.632 ± 0.054#	0.637 ± 0.069#
NAR+TMZ	0.75 ± 0.07	0.65 ± 0.069	0.673 ± 0.064	0.65 ± 0.047#	0.627 ± 0.049#	0.64 ± 0.053##

*Data were represented as mean ± SD (n=8). Sham (sham operated group), I/R (Ischemia-reperfusion + normal saline), NAR (I/R + NAR 100 mg/kg, i.p, for one week), TMZ (I/R + TMZ 5 mg/kg, iv, before reperfusion). NAR + TMZ, combination of NAR and TMZ. Repeated measure-Two-way ANOVA followed by Tukey's post hoc test. ***p<0.001, vs. sham group. #p<0.05, ##p<0.01, vs. I/R group.*

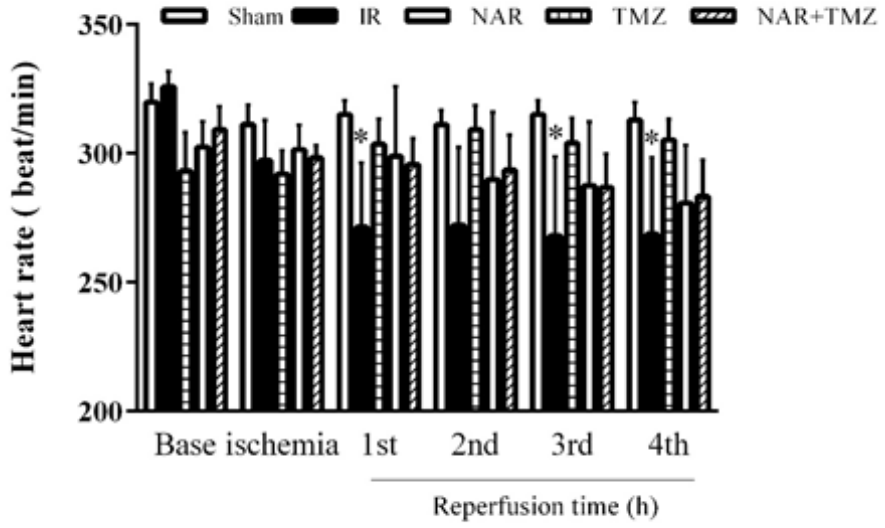


Figure 1 – *Effect of Naringin (NAR), Trimetazidine (TMZ) or their combination pretreatment on heart rate, following renal I/R (I/R). Data were represented as mean ± SD (n=8). Sham (sham operated group), I/R (Ischemia-reperfusion + normal saline), NAR (I/R + NAR 100 mg/kg, i.p, for one week), TMZ (I/R + TMZ 5 mg/kg, iv, before reperfusion). NAR + TMZ combination of NAR and TMZ. Repeated measure-Two-way ANOVA followed by Tukey's post hoc test. *p<0.05, vs. sham group.*

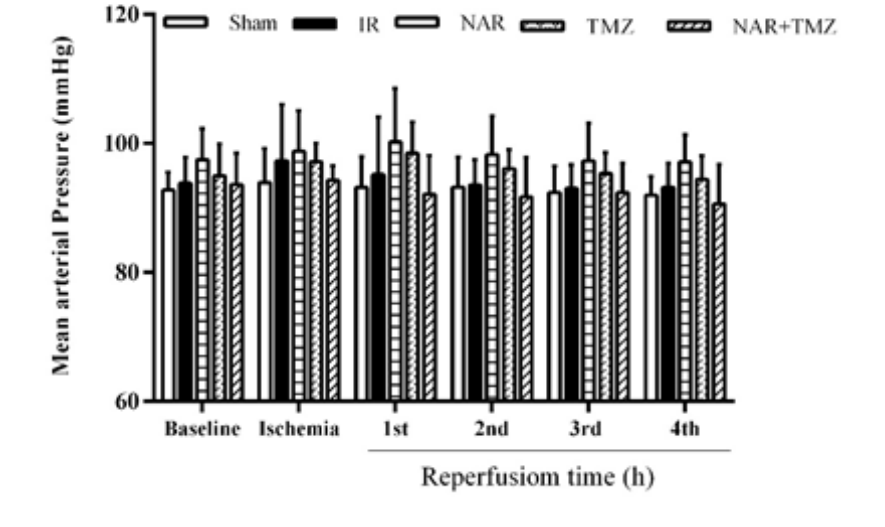


Figure 2 – *Effect of Naringin (NAR), Trimetazidine (TMZ) or their combination pretreatment on mean arterial pressure following renal I/R (I/R). Data were represented as mean ± SD (n=8). Sham (sham operated group), I/R (Ischemia-reperfusion + normal saline), NAR (I/R + NAR 100 mg/kg, i.p, for one week), TMZ (I/R + TMZ 5 mg/kg, iv, before reperfusion). NAR + TMZ, combination of NAR and TMZ. Repeated measure-Two-way ANOVA followed by Tukey's post hoc test.*

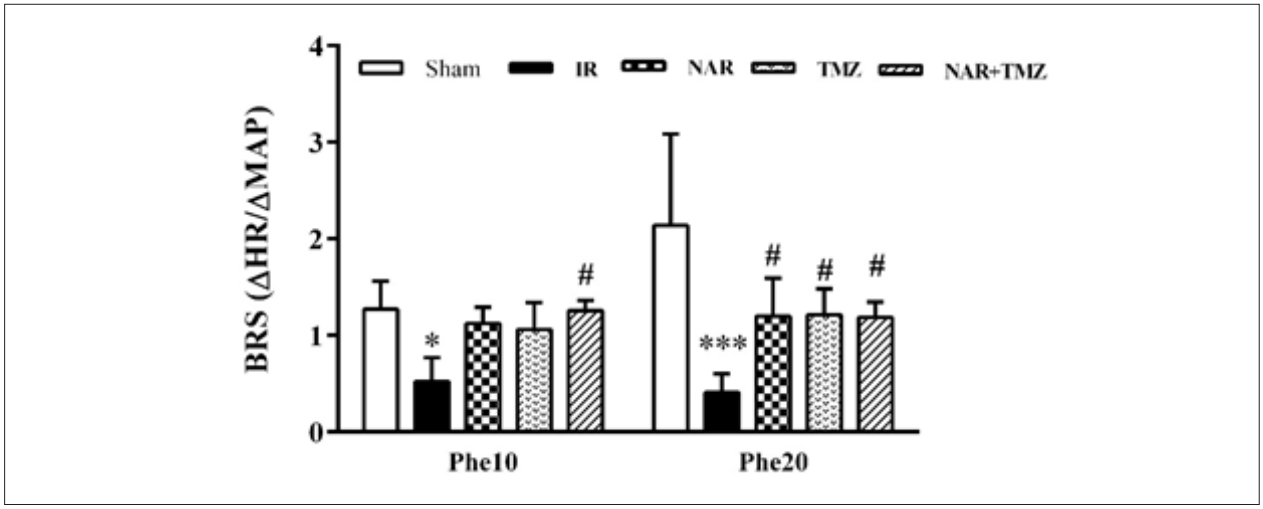


Figure 3 – *Effect of Naringin (NAR), Trimetazidine (TMZ) or their combination pretreatment on baroreceptor sensitivity (ΔHR/ΔMAP)) following renal I/R (I/R). Data were represented as mean ± SD (n=8). Sham (sham operated group), I/R (Ischemia-reperfusion + normal saline), NAR (I/R + NAR100 mg/kg, i.p, for one week), TMZ (I/R + TMZ 5 mg/kg, iv, before reperfusion). NAR + TMZ, combination of NAR and TMZ. Repeated measure-Two-way ANOVA followed by Tukey's post hoc test. *p<0.05, ***p<0.001, vs. sham group, #p< 0.05 vs. I/R group.*

beta-fatty acids, which leads to the production of ATP with less oxygen consumption.[11]

The results of this study showed BRS improvement with NAR and TMZ pretreatment in I/R. Although the precise mechanism of the antioxidant effects of NAR and TMZ on BRS is unclear in renal I/R, it is possible that NAR, TMZ or their combination increase BRS in renal I/R by improving the autonomic nervous system function. Recently, it has been shown that the administration of antioxidants can improve BRS by improving autonomic function.[24] The central mechanisms of NAR and TMZ need to be clarified in further studies on the autonomic nervous system function.[25]

The reduction in renal function leads to the accumulation of toxins and increased serum osmolality, which can directly stimulate vascular endothelial growth factor synthesis. In addition, the increase in ROS production leads to endothelial damage and permeability of the blood-brain barrier (BBB).[32,33] Several lines of studies have shown that BBB performance was disrupted in experimental models of AKI indicated by Evans blue dye over the permeability into the brain tissue.[34,35] On the other hand, experimental inflammatory models induced by alpha tumor necrosis factor (TNF-α) abnormally increases the permeability of the BBB. These experimental studies support the idea that inflammation associated with AKI elevates the inflammatory cytokines in the bloodstream and this can impair BBB permeability.[36] Extensive evidence showed that NAR is a potent antioxidant that crosses the BBB and reduces inflammatory factors to protect the brain.[37,38] A sudden drop in kidney function leads to toxin accumulation and increased serum osmolality, which can increase ROS, resulting in endothelial injury, BBB and brain transmitter disruption.[39]

An experimental study showed that cerebral I/R injury results in changes in cardiac electrophysiological parameters, as well as reduction in NTS electrical activity. However, the administration of anti-oxidants prevented these complications.[16] The reduction in oxygen availability to the neuronal system, followed by the ruptured blood vessels, led to a cascade of events, including activation of glutamate receptors and Ca^{2+} influx.[40] The activation of glutamate receptors caused an increase in cytoplasmic Ca^{2+} concentrations, as the result of Ca^{2+} influx through α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) and *N*-methyl-D-aspartate (NMDA) receptor channels, and voltage-dependent Ca^{2+} channels (VDCC). The opening of inotropic glutamate receptors, and the consequent influx of Na^{+} and Ca^{2+}, is identified as the first stages in the excitotoxic process.[40]

Another experimental study showed that AKI induced by renal I/R led to renal dysfunction and increased renal sympathetic nerve activity and increased norepinephrine concentrations, indicating the role of the sympathetic nervous system in the development of AKI.[41] Recently, the role of renal nerves in the renal I/R model showed that renal sympathetic nerve denervation improved renal function, reduced the response of inflammatory factors and apoptosis without changes in blood pressure.[42] While Mitaka et al. showed that renal I/R led to a reduction in blood pressure and no changes in heart rate, which is opposed to the results of this study.[43] This controversy may be related to the experimental model, the animal species and the reperfusion period. Our previous study indicated that renal I/R injury result in kidney dysfunction and myocardial injury and pre-treatment with NAR and TMZ alone or their combination might have a protective role on the remote effect of AKI on oxidative stress and myocardial injury through Nrf-2 regulation.[44]

Limitations

This study had some limitations. Firstly because it is part of a Ph.D. thesis, including financial and time limitations. Therefore, we could not identify some parameters such as brain histology and measurement of molecular and antioxidant

parameters in the brain tissue. Our aim was to investigate BRS and NTS activity in the AKI model.

Conclusion

Our findings, along with other research findings, are in line with the present study, which suggest the reduction in renal function due to renal I/R injury, leading to a reduction in BRS and NTS electrical activity. Probably, there is an association between renal function reduction and BRS decrease, although NAR and TMZ alone or their combination improved the BRS and the NTS electrical activity. However, it can be hoped that these antioxidant agents can be used to prevent renal I/R complications in areas beyond the injury site.

Acknowledgments

This article is a part of Ms. Negin Amini's Ph.D. thesis, who is a student at Ahvaz Jundishapur University of Medical Sciences. This work was supported by the Persian Gulf Physiology Research Center of Ahvaz Jundishapur University of Medical Sciences. The authors gratefully acknowledge the help and financial support of the Persian Gulf Research Center of Ahvaz Jundishapur University of Medical Sciences.

Author Contributions

Conception and design of the research: Amini N, Sarkaki A, Badavi M; Acquisition of data: Amini N; Analysis and interpretation of the data: Amini N, Dianat M, Mard SA, Ahangarpour A, Badavi M; Statistical analysis and Writing of the manuscript: Amini N, Badavi M; Critical revision of the manuscript for intellectual content: Sarkaki A, Dianat M, Mard SA, Ahangarpour A, Badavi M.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by The Persian Gulf Physiology Research Center of Ahvaz Jundishapur University of Medical Sciences.

Study Association

This article is part of the thesis of Doctoral submitted by Negin Amini, from Ahvaz Jundishapur University of Medical Sciences.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Ahvaz Jundishapur University of Medical Sciences under the protocol number IR.AJUMS.REC.1395.149. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

References

1. Trof RJ, Di Maggio F, Leemreis J, Groeneveld AJ. Biomarkers of acute renal injury and renal failure. Shock. 2006; 26 (3):245-53.
2. Leung AK, Yan WW. Renal replacement therapy in critically ill patients. Hong Kong Med J. 2009;15 (2):122-9.
3. Kosieradzki M, Rowinski W. Ischemia/reperfusion injury in kidney transplantation: mechanisms and prevention. Transplantation proc. 2008;40 (10): 3279-88.
4. Kalogeris T, Baines CP, Krenz M, Korthuis RJ. Cell biology of ischemia/reperfusion injury. Int Rev Cell Mol Biol. 2012; 298: 229-317. doi. org/10.1016/B978-0-12-394309-5.00006-7
5. Carden DL, Granger DN. Pathophysiology of ischaemia–reperfusion injury. J Pathol. 2000; 190(3): 255-66.
6. Dibona GF, Kopp UC. Neural control of renal function. Physiol Rev. 1997; 77(1): 75-197.
7. Kawabe T, Chitravanshi VC, Kawabe K, Sapru HN. Cardiovascular function of a glutamatergic projection from the hypothalamic paraventricular nucleus to the nucleus tractus solitarius in the rat. Neuroscience. 2008; 153(3): 605-17.
8. Kaur M, Chandran DS, Jaryal AK, Bhowmik D, Agarwal SK, Deepak KK. Baroreflex dysfunction in chronic kidney disease. World J Nephrol. 2016;5(1):53-65.
9. Singh D, Chopra K. The effect of naringin, a bioflavonoid on ischemia-reperfusion induced renal injury in rats. Pharmacolol Res. 2004;50(2):187-93.
10. Gaur V, Aggarwal A, Kumar A. Protective effect of naringin against ischemic reperfusion cerebral injury: possible neurobehavioral, biochemical and cellular alterations in rat brain. Eur J Pharmacol. 2009; 616(1-3):147-54.
11. Szwed H, Sadowski Z, Pachocki R, Domżał-Bocheńska M, Szymczak K, Szydłowski Z, et al. Proposed antiischemic effects of trimetazidine in coronary diabetic patients. A substudy from TRIMPOL-1. Cardiovasc Drugs Therap. 1999; 13 (3): 217-22.
12. Jassem W, Heaton ND. The role of mitochondria in ischemia/reperfusion injury in organ transplantation. Kidney Int. 2004;66(2):514-7.
13. Argaud L, Gomez L, Gateau-Roesch O, Couture-Lepetit E, Loufouat J, Robert D, et al. Trimetazidine inhibits mitochondrial permeability transition pore opening and prevents lethal ischemia-reperfusion injury. J Mol Cell Cardiol. 2005; 39(6): 893-9.
14. Grekas D, Dioudis C, Papageorgiou G, Iliadis S, Zilidis C, AlivanisP, et al. Lipid Peroxidation After Acute Renal Ischemia and Reperfusion in Rats: The Effect of Trimetazidine. Ren Fail. 1996;18(4): 545-52.
15. Cau J, Favreau F, Tillement JP, Lerman LO, Hauet T, Goujon JM. Trimetazidine reduces early and long-term effects of experimental renal warm ischemia: a dose effect study. J Vasc Surg. 2008; 47(4): 852-60.
16. Nejad KH, Dianat M, Sarkaki A, GharibNaseri MK, Badavi M, Farbood Y. Ellagic acid improves electrocardiogram waves and blood pressure against global cerebral ischemia rat experimental models.Electron physician. 2015;7(4): 1153-62.
17. Maleki M, Nematbakhsh M. Renal Blood Flow Response to Angiotensin 1-7 versus Hypertonic Sodium Chloride 7.5% Administration after Acute Hemorrhagic Shock in Rats. Int J Vas Med. 2016;2016: 6562017. Doi: 10.1155/2016/6562017
18. Nesic Z, Todorovic Z, Stojanovic R, Basta-Jovanovic G, Radojevic-Skodric S, Velickovic R, et al. Single-dose intravenous simvastatin treatment attenuates renal injury in an experimental model of ischemia-reperfusion in the rat. J Pharmacol Sci. 2006; 102(4): 413-7.

19. Azadbakht MK, Nematbakhsh M. Angiotensin 1-7 administration alters baroreflex sensitivity and renal function in sympathectomized rats. J Nephropathol. 2017;7(2):79-82.

20. Franczyk-Skora B, Gluba-Brzozka A, Wranicz JK, Banach M, Olszewski R, Rysz J. Sudden cardiac death in CKD patients. Int Urol Nephrol. 2015; 47(6): 971-82.

21. Tu H, Zhang D, Li Y-L. Cellular and molecular mechanisms underlying arterial baroreceptor remodeling in cardiovascular diseases and diabetes. Neurosci Bull. 2019;35(1):98-112.

22. Andres-Hernando A, Dursun B, Altmann C, Ahuja N, He Z, Bhargava R, et al. Cytokine production increases and cytokine clearance decreases in mice with bilateral nephrectomy, Nephrol Dial Transplant. 2012; 27(12):4339-4347.

23. Chen J, Hartono JR, John R, Bennett M, Zhou XJ, Wang Y, et al. Early interleukin 6 production by leukocytes during ischemic acute kidney injury is regulated by TLR4. Kidney Int. 2011; 80(5): 504-15.

24. Monteiro MM, Franca-Silva MS, Alves NF, Porpino SK, Braga VA. Quercetin improves baroreflex sensitivity in spontaneously hypertensive rats. Molecules. 2012; 17(11): 12997-3008.

25. Botelho-Ono MS, Pina HV, Sousa KH, Nunes FC, Medeiros IA, Braga VA. Acute superoxide scavenging restores depressed baroreflex sensitivity in renovascular hypertensive rats. Auton Neurosci. 2011; 159(1-2): 38-44.

26. Li Z, Mao HZ, Abboud FM, Chapleau MW. Oxygen-derived free radicals contribute to baroreceptor dysfunction in atherosclerotic rabbits. Circ Res. 1996; 79(4): 802-11.

27. Amini N, Sarkaki A, Dianat M, Mard SA, Ahangarpour A, Badavi M. The renoprotective effects of naringin and trimetazidine on renal ischemia/reperfusion injury in rats through inhibition of apoptosis and down regulation of micoRNA-10a. Biom Pharmacother. 2019; 112: 108568. DOI: 10.1016/j.biopha.2019.01.029

28. Queiroz TM, Guimaraes DD, Mendes-Junior LG, Braga VA. alpha-lipoic acid reduces hypertension and increases baroreflex sensitivity in renovascular hypertensive rats. Molecules. 2012;17(11): 13357-67.

29. Chapleau MW, Cunningham JT, Sullivan MJ, Wachtel RE, Abboud FM. Structural versus functional modulation of the arterial baroreflex. Hypertension. 1995;26 (2): 341–7.

30. Ikemura M, Sasaki Y, Giddings JC, Yamamoto J. Preventive effects of hesperidin, glucosyl hesperidin and naringin on hypertension and cerebral thrombosis in stroke-prone spontaneously hypertensive rats. Phytother Res. 2012; 26(9): 1272-7.

31. Belardinelli R, Solenghi M, Volpe L, Purcaro A. Trimetazidine improves endothelial dysfunction in chronic heart failure: an antioxidant effect. Eur Heart Journal. 2007; 28(9):1102-8.

32. Chi OZ, HunterC, Liu X, Tan T, Weiss HR. Effects of VEGF on the blood-brain barrier disruption caused by hyperosmolarity. Pharmacology. 2008; 82(3):187-92.

33. Sadik NA, Mohamed WA, Ahmed MI. The association of receptor of advanced glycated end products and inflammatory mediators contributes to endothelial dysfunction in a prospective study of acute kidney injury patients with sepsis. Mol Cell Biochem. 2012; 359(1-2): 73-81.

34. Tso N, Hsu HP, Wu CM, Liu CC, Lei HY. Tumour necrosis factor-α causes an increase in blood-brain barrier permeability during sepsis. J Med Microbiol. 2001;50(9): 812-21.

35. Liu M, Liang Y, Chigurupati S, Lathia JD, Pletnikov M, Z Sun, et al. Acute kidney injury leads to inflammation and functional changes in the brain. J Am Soc of Nephrol. 2008;19(7): 1360-70.

36. Prieto I, Martinez JM, Hermoso F, Ramirez MJ, Vargas F, De Gasparo M, et al. Oral administration of losartan influences aminopeptidase activity in the frontal cortex. Eur Neuropsychopharmacol. 2000;10(4): 279-82.

37. Zbarsky V, Datla KP, Parkar S, Rai DK, Aruoma OI, Dexter DT. Neuroprotective properties of the natural phenolic antioxidants curcumin and naringenin but not quercetin and fisetin in a 6-OHDA model of Parkinson's disease. Free Radic Res. 2005; 39(10):1119-25.

38. Tsai TH. Determination of naringin in rat blood, brain, liver, and bile using microdialysis and its interaction with cyclosporin a, a p-glycoprotein modulator. J Agric Food Chem. 2002;50(23): 6669-74.

39. Nongnuch A, Panorchan K, Davenport A. Brain–kidney crosstalk. Crit Care. 2014;18(3): 225. doi: 10.1186/cc13907.

40. Mattson MP. Excitotoxic and excitoprotective mechanisms: abundant targets for the prevention and treatment of neurodegenerative disorders. Neuromolecular Med. 2003; 3(2): 65-94.

41. Fujii T, Kurata H, Takaoka M, Muraoka T, Fujisawa Y, Shokoji T, et al. The role of renal sympathetic nervous system in the pathogenesis of ischemic acute renal failure. Eur J Pharmacol. 2003; 481(2-3):241-8.

42. Kim J, Padanilam BJ. Renal denervation prevents long-term sequelae of ischemic renal injury. Kidney Int. 2015; 87(2): 350-8.

43. Mitaka C, Si MK, Tulafu M, Yu Q, Uchida T, Abe S, et al. Effects of atrial natriuretic peptide on inter-organ crosstalk among the kidney, lung, and heart in a rat model of renal ischemia-reperfusion injury, Intensive Care Med. 2014;2(1):28. doi: 10.1186/s40635-014-0028-8.

44. Amini N, Dianat M, Mard SA, Ahangarpour A, Badavi M. Protective effects of naringin and trimetazidine on remote effect of acute renal injury on oxidative stress and myocardial injury through Nrf-2 regulation. Pharmacol Rep. 2019;71(6): 1059-1066.

Original Article

Naringin, Trimetazidine and Baroreflex in Renal Ischemia-Reperfusion Injury

Luis Cuadrado Martin[1]

Universidade Estadual Paulista,[1] *Botucatu, SP - Brazil*

Short Editorial related to the article: Naringin and Trimetazidine Improve Baroreflex Sensitivity and Nucleus Tractus Solitarius Electrical Activity in Renal Ischemia-Reperfusion Injury

The paper "Naringin and trimetazidine improve baroreflex sensitivity and electrical activity of solitary tract nucleus in renal ischemia-reperfusion injury," published in this journal,[1] found improvement in baroreflex sensitivity in an acute ischemia/reperfusion kidney injury model in rats treated by naringin and/or trimetazidine.

Trimetazidine and naringin are substances capable of reducing oxidative stress, documented in many situations. Trimetazidine is a drug with anti-ischemic properties, which acts directly on mitochondria and is able to decrease oxidative stress. Naringin is a polyphenol with antioxidant properties present in several citrus fruits.

Oxidative stress is involved in multiple pathophysiological processes.[2] On the other hand, disorder of the baroceptor reflex is involved in the pathogenesis of hypertension[3,4] and heart failure.[5] Moreover, this disorder plays a role in chronic kidney disease[6] and in acute kidney injury.[7] The solitary tract nucleus plays a fundamental role in the baroceptor reflex integration and its action is influenced by oxidative stress.[7]

Attenuation of the baroreflex in acute kidney injury can make it difficult to respond to hemodynamic instability during an episode of acute kidney injury.[8,9] Acute kidney injury also shows an increase in oxidative stress.[2] Free radicals and reactive oxygen species are produced in abundance in kidney damage due to ischemia/reperfusion and flood the circulatory system causing undesirable effects on various organs, including the solitary tract, which, as we have seen, is an important integrator of the baroreflex activity.

In other models, except acute kidney injury, oxidative stress is correlated with dysfunction of the baroceptors and antioxidants improved their function. Nevertheless, in acute kidney injury, whether this increase in oxidative stress has a cause-and-effect relationship with baroreflex attenuation is controversial. Thus, if, in models of acute kidney injury, by blocking oxidative stress, we could restore the baroreflex, it would be evident that oxidative stress plays this postulated role.

The variation in heart rate to mean arterial pressure ratio compared to the challenge with phenylephrine was the baroreflex index performed in the study of Amini et al.[1] Using a stereotactic technique, before inducing acute kidney injury, an electrode was implanted in the solitary tract nucleus of the rats with nucleus activity.[1] Thus, in addition to improvement of the baroreflex, there was a reversal of solitary tract nucleus activity attenuation that had been documented concurrently with the reperfusion injury.

These results have pathophysiological implications, insofar as they demonstrate the participation of oxidative stress in the dysfunction of the solitary tract nucleus and consequently of the baroreflex in acute kidney injury, as well as therapeutic implications, since it encourages work with these drugs in order to mitigate the complications of acute kidney injury in humans,[9-11] a clinical situation that denotes an ominous prognosis.[12] Therefore, this line of research may help understand the treatment in humans with this nosological entity. It is of note that there is evidence of prophylaxis of contrast nephropathy using trimetazidine in humans.[13,14]

Keywords

Flavanones; Flavonoids; Trimetazidine; Vasodilatador Agents; Hypertension; Heart Failure; Renal Reperfusion; Oxidative Stress.

Mailing Address: Luis Cuadrado Martin •
UNESP - Clínica Médica - Prof. Montenegro, s/n. Postal Code 18600-000, Botucatu, SP – Brazil
E-mail: l.martin@unesp.br

DOI: https://doi.org/10.36660/abc.20210453

References

1. Amini N, Sarkaki A, Dianat M, Mard SA, Ahangarpour A, Badavi M. Naringin and Trimetazidine Improve Baroreflex Sensitivity and Nucleus Tractus Solitarius Electrical Activity in Renal Ischemia-Reperfusion Injury. Arq Bras Cardiol. 2021; 117(2):290-297. doi: https://doi.org/10.36660/abc.20200121
2. Grams ME, Rabb H. The distant organ effects of acute kidney injury. Kidney Int. 2012;81(10):942-8.
3. Valenti VE, Ferreira C, Meneghini A, Ferreira M, Murad N, Ferreira Filho C, et al. Evaluation of baroreflex function in Young spontaneously hypertensive rats. Arq Bras Cardiol. 2009;92(3):205-15.
4. Sousa LE, Favero IFD, Bezerra FS, Souza ABF, Alzamora AC. Environmental Enrichment Promotes Antioxidant Effect in the Ventrolateral Medulla and Kidney of Renovascular Hypertensive Rats. Arq Bras Cardiol. 2019;113(5):905-12.
5. Guimarães GV, Belli JF, Bacal F, Bocchi EA. Behavior of central and peripheral chemoreflexes in heart failure. Arq Bras Cardiol. 2011;96(2):161-7.
6. Quarti-Trevano F, Seravalle G, Dell'Oro R, Mancia G, Grassi G. Autonomic Cardiovascular Alterations in Chronic Kidney Disease: Effects of Dialysis, Kidney Transplantation, and Renal Denervation. Curr Hypertens Rep. 2021;23(2):10.
7. Abdulla MH, Johns EJ. The innervation of the kidney in renal injury and inflammation: a cause and consequence of deranged cardiovascular control. Acta Physiol (Oxf). 2017;220(4):404-16.
8. Chen WW, Xiong XQ, Chen Q, Li YH, Kang YM, Zhu GQ. Cardiac sympathetic afferent reflex and its implications for sympathetic activation in chronic heart failure and hypertension. Acta Physiol (Oxf). 2015;213(4):778-94.
9. Verney C, Legouis D, Voiriot G, Fartoukh M, Labbé V. Inappropriate Heart Rate Response to Hypotension in Critically Ill COVID-19-Associated Acute Kidney Injury. J Clin Med. 2021;10(6):1317.
10. Ranucci M, Porta A, Bari V, Pistuddi V, La Rovere MT. Baroreflex sensitivity and outcomes following coronary surgery. PLoS One. 2017 Apr 6;12(4):e0175008.
11. Huyut MA. Kidney Injury Molecule-1 Is Associated with Contrast-Induced Nephropathy in Elderly Patients with Non-STEMI. Arq Bras Cardiol. 2021;116(6):1048-56.
12. Barbosa RR, Cestari PF, Capeletti JT, Peres GM, Ibañez TL, da Silva PV, Farran JA, Amato VL, Farsky PS. Impact of renal failure on in-hospital outcomes after coronary artery bypass surgery. Arq Bras Cardiol. 2011;97(3):249-53.
13. Fu H, Zhang J, Zhang H, Zhang P, Fu X, Zeng Z, et al. Trimetazidine can prevent the occurrence of contrast-induced nephropathy after percutaneous coronary intervention in elderly patients with renal insufficiency. Perfusion. 2020;10:267659120957856.
14. Heshmatzadeh Behzadi A, Amoozgar B, Jain S, Velasco N, Zahid U, Abbasi H, et al. Trimetazidine reduces contrast-induced nephropathy in patients with renal insufficiency undergoing coronary angiography and angioplasty: A systematic review and meta-analysis (PRISMA). Medicine (Baltimore). 2021;100(10):e24603.

Characteristics and Temporal Trends in the Mortality of Different Heart Failure Phenotypes in Primary Care

Antonio José Lagoeiro Jorge,[1] Leticia Mara dos Santos Barbetta,[1] Eduardo Thadeu de Oliveira Correia,[1] Wolney de Andrade Martins,[1] Adson Renato Leite,[1] Maria Auxiliadora Nogueira Saad,[1] Márcia Maria Sales dos Santos,[1] Dayse Mary Correia,[1] Maria Luiza Garcia Rosa,[1] Sérgio Chermont,[1] Cárita Cunha dos Santos,[1] Evandro Tinoco Mesquita[1,2]

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

C.T.E.B, UHG,[2] - Brazil

Abstract

Background: **The classification of heart failure (HF) by phenotypes has a great relevance in clinical practice.**

Objective: **The study aimed to analyze the prevalence, clinical characteristics, and outcomes between HF phenotypes in the primary care setting.**

Methods: **This is an analysis of a cohort study including 560 individuals, aged ≥ 45 years, who were randomly selected in a primary care program. All participants underwent clinical evaluations, b-type natriuretic peptide (BNP) measurements, electrocardiogram, and echocardiography in a single day. HF with left ventricular ejection fraction (LVEF) < 40% was classified as HF with reduced ejection fraction (HFrEF), LVEF 40% to 49% as HF with mid-range ejection fraction (HFmrEF) and LVEF ≥ 50% as HF with preserved ejection fraction (HFpEF). After 5 years, the patients were reassessed as to the occurrence of the composite outcome of death from any cause or hospitalization for cardiovascular disease.**

Results: **Of the 560 patients included, 51 patients had HF (9.1%), 11 of whom had HFrEF (21.6%), 10 had HFmrEF (19.6%) and 30 had HFpEF (58.8%). HFmrEF was similar to HFpEF in BNP levels ($p < 0.001$), left ventricular mass index ($p = 0.037$), and left atrial volume index ($p < 0.001$). The HFmrEF phenotype was similar to HFrEF regarding coronary artery disease ($p = 0.009$). After 5 years, patients with HFmrEF had a better prognosis when compared to patients with HFpEF and HFrEF ($p < 0.001$).**

Conclusion: **The prevalence of ICFEI was similar to that observed in previous studies. ICFEI presented characteristics similar to ICFEP in this study. Our data show that ICFEi had a better prognosis compared to the other two phenotypes.**

Keywords: **Heart Failure/trends; Heart Failure/mortality; Prevalence; Primary Health Care; Prognosis; Eidemiology; Stroke Volume.**

Introduction

The classification of heart failure (HF) by phenotypes has great relevance in clinical practice, since they differ in relation to the characteristics, prognosis, and treatment of the patient.[1] Classically, two phenotypes of HF were described in guidelines, namely, HF with reduced ejection fraction (HFrEF) where left ventricular ejection fraction (LVEF) is less than 50% and HF with preserved ejection fraction (HFpEF) with LVEF ≥ 50%.[2] In 2013, the American College of Cardiology Foundation/American Heart Association published new guidelines for HF, in which patients with LVEF between 41% and 50% were classified as borderline HFpEF.[3] In 2016, the HF guidelines of the European Society of Cardiology recognized HF with LVEF between 40% and 49% as a distinct phenotype, called HF with mid-range ejection fraction (HFmrEF).[4] Finally, in 2018, the Brazilian Society of Cardiology added HFmrEF to the 2018 Chronic and Acute Heart Failure Guidelines.[5]

Recent studies have observed that the prevalence of patients with HFmrEF ranged from 13% to 24% of all patients with HF.[6-8] Current data from HF studies indicates that HFmrEF presents intermediate characteristics.[8] Moreover, a meta-analysis that included more than 600,000 patients with HF concluded that patients with HFmrEF had lower all-cause mortality than HFrEF patients and no statistical difference from patients with HFpEF. Regarding all-cause hospitalization, there was no statistical difference between all the three HF phenotypes.[9] There are no studies in Brazil that have evaluated this phenotype in primary care. Therefore, the present study aimed to analyze the prevalence and the clinical characteristics of HFmrEF, as well as the outcomes among HF phenotypes in patients from a primary care setting.

Mailing Address: Antonio José Lagoeiro Jorge •
Universidade Federal Fluminense - Rua Marques de Paraná, 303. Postal Code 24033-900, Centro, Niterói, RJ – Brazil
E-mail: lagoeiro@globo.com
Manuscript received December 28, 2019, revised manuscript June 25, 2020, accepted August 12, 2020.

DOI: https://doi.org/10.36660/abc.20190912

Methods

This cohort study included, at the baseline, 633 individuals aged ≥ 45 years, who were registered in the Primary Care Program of the city of Niterói, a medium-sized city with 487,562 inhabitants in the state of Rio de Janeiro, Brazil. The Primary Care Program offers coverage to 137,463 residents in 32 service modules, divided into 110 sectors. Initially, 21 sectors were selected through a random sequence, generated by a computer program, in which the weight of each sector was proportional to the number of individuals.[10] The data were collected from July 2011 to December 2012. After 5 years, the patients in this study were reassessed as to the occurrence of the composite outcome of death from any cause or hospitalization for cardiovascular disease. During the follow-up, there were 73 (11.5%) losses, and the final number of individuals assessed was 560.

Population

The survey sample size was estimated based on a minimum HF prevalence of 6%, with an absolute error of 2% (confidence interval [CI] = 99%, 4% to 8%). This assumption required a sample size of 580 individuals. In each one of the 21 sectors included, 30 individuals between 45 and 100 years of age were randomly chosen. Another 20 individuals per unit were also chosen to allow replacement in case of impossibility of participation, totaling 1,050 selected individuals. In this manner, we sent letters to health unit staff to invite 1,050 individuals to participate in this study, and 666 of these individuals attended the visit and signed the consent form. Thirty-three individuals who did not complete all of the research procedures were excluded. The baseline population was 633 individuals, 73 (11.5%) of whom were not located after 5 years and were subsequently excluded. The final population was 560 individuals. (Figure 1)

The choice of the primary care units and the number of individuals in each unit were planned in order to represent the demographic distribution. The selection of subjects was carried out through a random sequence generated by a computer program. The inclusion criteria were age ≥ 45 years and willingness to provide informed consent. Whenever there was a refusal, the next subject in the randomized list was invited to participate.

All participants in the study underwent a single-day evaluation that consisted of the following: (a) anamnesis and clinical examinations; (b) laboratory tests, including b-type natriuretic peptide (BNP) dosage; (c) 12-lead electrocardiogram (ECG); and (d) tissue Doppler echocardiography. ECG was performed in 12 simultaneous leads. Tissue Doppler echocardiography was performed by two certified physicians, using two portable devices, the Acuson Cypress 20 (Siemens, USA) and the AU-3 Partner (Esaote, Italy). The physicians were blinded from the clinical status and exam results. The exams were performed according to the recommendations of the quantification of chambers from the American

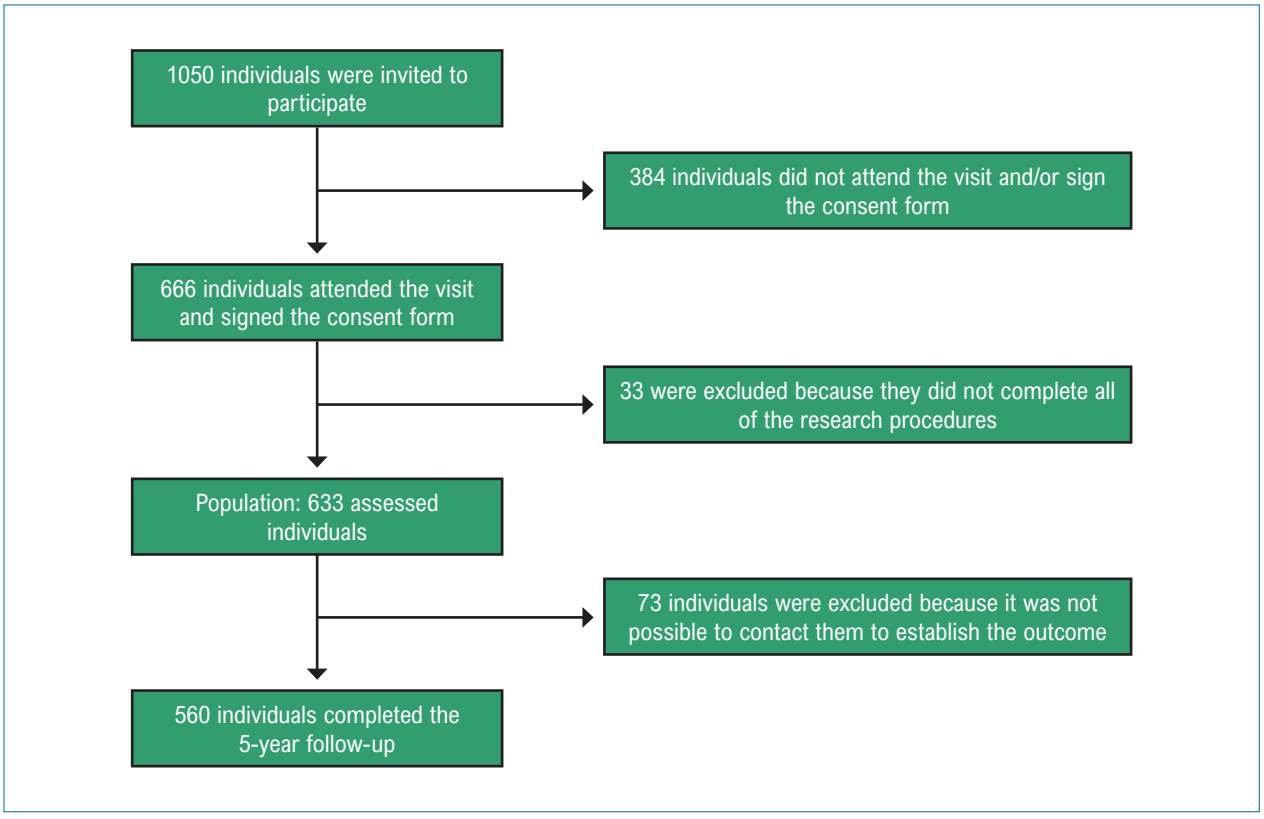


Figure 1 – *Population selection flowchart.*

Society of Echocardiography and the European Association of Echocardiography.[11] Systolic function was assessed by measuring LVEF using Simpson's method.

Definition of heart failure phenotypes

Diagnosis of HFrEF was confirmed in individuals with a history of HF or the presence of signs or symptoms of HF and LVEF < 40%. Diagnosis of HFpEF was confirmed in individuals with a history of HF or signs or symptoms of HF with LVEF ≥ 50% and end-diastolic volume index (EDVI) < 97 mL/m^2, in the presence of diastolic dysfunction of the left ventricle and BNP > 35 pg/mL. HFmrEF was confirmed in individuals with a history of HF or signs or symptoms of HF with LVEF between 40% and 49% and BNP > 35 pg/mL.[4,12]

Statistical analysis

Continuous variables were expressed as median and interquartile range, as none of them were positive for normality when tested using the Kolmogorov-Smirnov test. Categorical variables were summarized as absolute and relative frequencies. Regarding quantitative variables, differences between HF phenotypes were tested with the non-parametric tests (Mann-Whitney and Kruskal-Wallis), while categorical variables were assessed by chi-squared test. A Kaplan-Meier curve was estimated for the composite outcomes of the four possibilities (HF-free, HFrEF, HFmrEF, and HFpEF). The difference between the four curves and between HFmrEF and HF-free were tested with the log rank test. P values < 0.05 were considered statistically significant. All statistical analysis was performed with SPSS software version 23.0 (Chicago, Illinois, USA).

Ethical considerations

This study was conducted in accordance with the principles of the Declaration of Helsinki revised in 2000. The study protocol was approved by the institution's Ethics Committee under number 0077.0.258.000-10.

Results

Prevalence and characteristics of patients with HFmrEF

Of the 560 patients included in the study, 509 were not diagnosed with HF (90.9%), and 51 were diagnosed with HF (9.1%). Of the 51 patients with HF, 11 had HFrEF (21.6%), 10 had HFmrEF (19.6%), and 30 had HFpEF (58.8%). The demographic and clinical characteristics of patients with HF are shown in Table 1. HFmrEF was similar to HFpEF in left ventricular mass index (LVMI) and left atrial volume index (LAVI). We observed more coronary artery disease in patients with the HFrEF phenotype, compared to HFmrEF. The percentage of chronic kidney disease was intermediate in the HFmrEF group, being lower than HFpEF and higher than HFrEF. The HFmrEF group had intermediate values in following characteristics: heart rate, glucose levels, and creatinine-albumin ratio. However, there was no statistical difference among the groups with HF in these characteristics.

When analyzing the echocardiography parameters, the mean E/e' ratio, LVMI, LAVI, and EDVI showed statistical difference in overall analysis, with p < 0.001 in all analyses. The LVMI, LAVI, and EDVI showed intermediate values in HFmrEF. The LVMI in HFmrEF was lower than in HFrEF and similar to HFpEF. The LAVI in HFmrEF was significantly lower than HFrEF and similar to HFpEF. The EDVI was higher in HFmrEF when compared to HFpEF and lower when compared to HFrEF. Moreover, when the mean E/e' ratio in HFmrEF and HFrEF were analyzed separately, the E/e' ratio of the HFmrEF group was lower than that of the HFrEF group. (Table 2)

Prognosis of HF phenotypes

After 5 years, 64 composite outcomes occurred, namely, 50 deaths and 14 hospitalizations for cardiovascular disease. In the Kaplan-Meier curve (Figure 2), patients with HFmrEF had a worse composite outcome of all-cause death and cardiovascular hospitalization than patients without HF. However, patients with HFmrEF had a better prognosis in the Kaplan-Meier analysis, when compared to patients with HFpEF and HFrEF, whereas patients with HFpEF had better prognosis than those with the HFrEF phenotype. Table 3 shows the means and their confidence intervals of survival for the different HF phenotypes.

Discussion

Since the adoption of HFmrEF as a new phenotype of HF, the major challenge has been to define the baseline characteristics, pathophysiology, and treatment for this new group of patients. The present article is the first study of HFmrEF in a Brazilian population, involving primary care patients. We conducted an analysis of the Digitalis study[10] in order to evaluate the prevalence and the clinical and echocardiographic characteristics of patients with HFmrEF in Brazil.

In our population of patients with HF, the prevalence of HFmrEF was 22%, similar to other studies.[6-8]

The studies by Rickenbacher et al.[12] and Tsuji et al.[7] showed that BNP levels were intermediate in HFmrEF. However, in our study, BNP in the HFmrEF group did not present intermediate values; it was similar to HFpEF, and it showed lower values than in HFrEF. However, regarding the prevalence of ischemic etiology in the HFmrEF group, our study showed that HFmrEF was similar to HFrEF, similar to previous studies. Results from the study by Kapoor et al.[6] and the Swedish-HF registry[11] suggest that ischemic etiology is distinctly more common in HFrEF and HFmrEF. The TOPCAT study[13] evaluated the use of spironolactone in patients with different LVEF ranges and showed that there was a reduction in hospitalizations in patients with HF, especially those with LVEF between 45% and 50%. In the CHARM study,[14] it was concluded that the use of candesartan improved the outcomes for HFmrEF as well as HFrEF. Thus, by extrapolation, HFmrEF could respond to the recommended treatment for HFrEF of ischemic etiology, as suggested by the HF guidelines.[3,5]

When analyzing the parameters of Doppler echocardiography, the LVMI, LAVI, and the E/e' ratio, in the HFmrEF group, were similar to HFpEF, while the EDVI

Table 1 – Demographic and clinical characteristics of patients with heart failure, according to phenotype HFpEF, HFmrEF, or HFpEF

	HF-free (n=509)	HFrEF (n=11)	HFmrEF (n=10)	HFpEF (n=30)	Overall	HFrEF vs. HFmrEF	HFpEF vs. HFmrEF	HFrEF vs. HFpEF
Male sex (%)	37	64	40	27	0.190	0.279	0.426	0.029
Age, years (median)	57(51-64)	74(57-78)	72(60-79)	72.5(64.7-81.7)	<0.001	0.809	0.708	0.871
BMI (median)	27.2(24.5-30.8)	24.9(21.3-25.9)	28.1(26.3-30.6)	26.9(22.0-30.7)	0.156	0.057	0.319	0.496
HR, bpm (median)	70.5(63.2-77.5)	69(55.5-72.5)	72 (62.1-79.1)	76.5(63.2-84.7)	0.360	0.324	0,573	0.108
Systolic BP, mmHg (median)	133.3(121-147.5)	146(116-161)	130(117.9-157.8)	151.7(135.2-179.7)	0.001	0.751	0.032	0.168
Diastolic BP, mmHg (median)	82(74.1-90)	80(68.3-88.5)	77.5(71.1-90.9)	83.7(72.7-91.3)	0.699	0.778	0.699	0.310
BNP, pg/mL (median)	15(10-25)	306(153-615)	61.5(51-95)	87.5(52.7-120.5)	<0.0001	0.002	0.281	0.001
Glucose, mg/dL (median)	100(91-113)	103(84-119)	97(87-106.2)	100(94.7-119)	0.765	0.621	0.288	0.757
Uric acid, mg/dL (median)	5.1(4.2-6.1)	6.3(4.6-8.0)	5.2(4.9-6.5)	5.1(4.1-6.7)	0.192	0.398	0.430	0.108
Total cholesterol, mg/dL (median)	213(186-244)	185(177-253)	199(180-240)	208(196-231)	0.629	0.623	0.453	0.502
Triglycerides, mg/dL (median)	118(86-169)	115(86-190)	106(66-152)	101(90-136)	0.481	0.571	0.851	0.482
Hemoglobin, g/dL (median)	13.7(12.8-14.7)	13.9(13.4-16.4)	13.7(12.1-14.3)	13.9(12.6-14.7)	0.396	0.204	0.370	0.435
Microalbuminuria, mg/L (median)	11.2(5.9-23.4)	29.5(10.1-58.7)	11.1(3.9-31.1)	14.3(6.6-38.3)	0.265	0.178	0.457	0.371
eGFR, mL/min/1.73m² (median)	83.5(71.6-96.1)	76.3(47-103.1)	84.1(52.7-100.7)	69.4(50.5-89.1)	0.009	0.888	0.303	0.427
CAR, mg/g (median)	9.7(5.6-22.4)	40.1(7.8-78.5)	19.8(5.9-33.3)	15.7(8.6-45.2)	0.051	0.270	0.821	0.385
Diabetes (%)	24	27	0	27	0.341	0.074	0.068	0.969
Hypertension (%)	70	91	90	90	0.028	0.943	1.000	0.931
CAD (%)	7.5	27	10	27	0.001	0.314	0.274	0.969
CKD (%)	8.9	27.3	40	33.3	<0.0001	0.537	0.702	0.712
ACEI/ARB (%)	38	64	70	47	0.184	0.757	0.411	0.565
Beta-blockers (%)	14	36	30	30	0.012	0.757	1.000	0.698
Diuretics (%)	34	36	50	53	0.148	0.528	0.855	0.335
Composite outcome, n (%)	39 (7.7)	7(63.6)	3(30)	15(50)	<0.0001	0.123	0.271	0.438

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; BMI: body mass index; BNP: type B natriuretic peptide; BP: blood pressure; bpm: beats per minute; CAD: coronary artery disease; CAR: creatinine-albumin ratio; CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; HF: heart failure; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HR: heart rate. Categorical variables are shown as percentage (%) and continuous variables as median and interquartile range (25% and 75%); overall p value for continuous variables were calculated using the Kruskal-Wallis test; differences between HFpEF, HFmrEF, and HFrEF were calculated using the Mann-Whitney test; p values for categorical variables were calculated using Pearson's chi-square.

in HFmrEF showed intermediate values, with statistical differences when compared to HFpEF and HFrEF. The study by Rastogi et al.[15] suggests that patients with HFmrEF are a heterogeneous group, with at least 3 subgroups based on LVEF, namely, patients with previous LVEF < 40% (recovered ejection fraction), patients with previous LVEF > 50% (deteriorated ejection fraction), and patients with previous LVEF between 40% and 50% (unchanged ejection fraction). These findings reinforce the idea that the physiopathology of HFmrEF may have a contribution of systolic dysfunction and a contribution of diastolic dysfunction, as suggested by the 2016 European Society of Cardiology guidelines.[4]

Table 2 – Clinical characteristics of patients with heart failure, according to phenotype HFpEF, HFmrEF, or HFpEF

	HF-free (n=509)	HFrEF (n=11)	HFmrEF (n=10)	HFpEF (n=30)	Overall	HFrEF vs. HFmrEF	HFpEF vs. HFmrEF	HFrEF vs. HFpEF
Ejection fraction, %	61(58-65)	29(23-33)	43.5(41-48)	59.5(56.7-64.2)	<0.0001	<0.0001	<0.0001	<0.0001
Mean E/e' ratio, (±SD)	6.5(5.4-7.8)	9.6(7.5-17)	8.3(6-9.1)	7.9(6.1-12.1)	<0.0001	0.149	0.791	0.162
LAVI, ml/m², (±SD)	20.9(17.3-24.5)	38.6(26.8-65.9)	30.5(18.9-42.2)	29.4(24.3-41.8)	<0.0001	0.231	0.607	0.188
LVMI, g/m², (±SD)	89.3(76.5-102.8)	160.2(113.1-187.3)	119.0(102.9-154.0)	104.2(76.9-127.1)	<0.0001	0.091	0.123	0.002
EDVI, ml/m², (±SD)	62.8(54.5-71.2)	106.0(82.5-150.3)	93.8(75.6-114.3)	68.7(54.2-76.2)	<0.0001	0.360	<0.0001	0.001

E: early mitral inflow velocity; E´: mitral annular early diastolic velocity; EDVI: end-diastolic volume index; HF: heart failure; HFmrEF: heart failure with mid-range ejection fraction; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LAVI: left atrial volume index; LVMI: left ventricular mass index. Data are shown as median and interquartile range (25% and 75%); (*) overall p value were calculated using the Kruskal-Wallis test; differences between HFpEF, HFmrEF and HFrEF were calculated using the Mann-Whitney test.

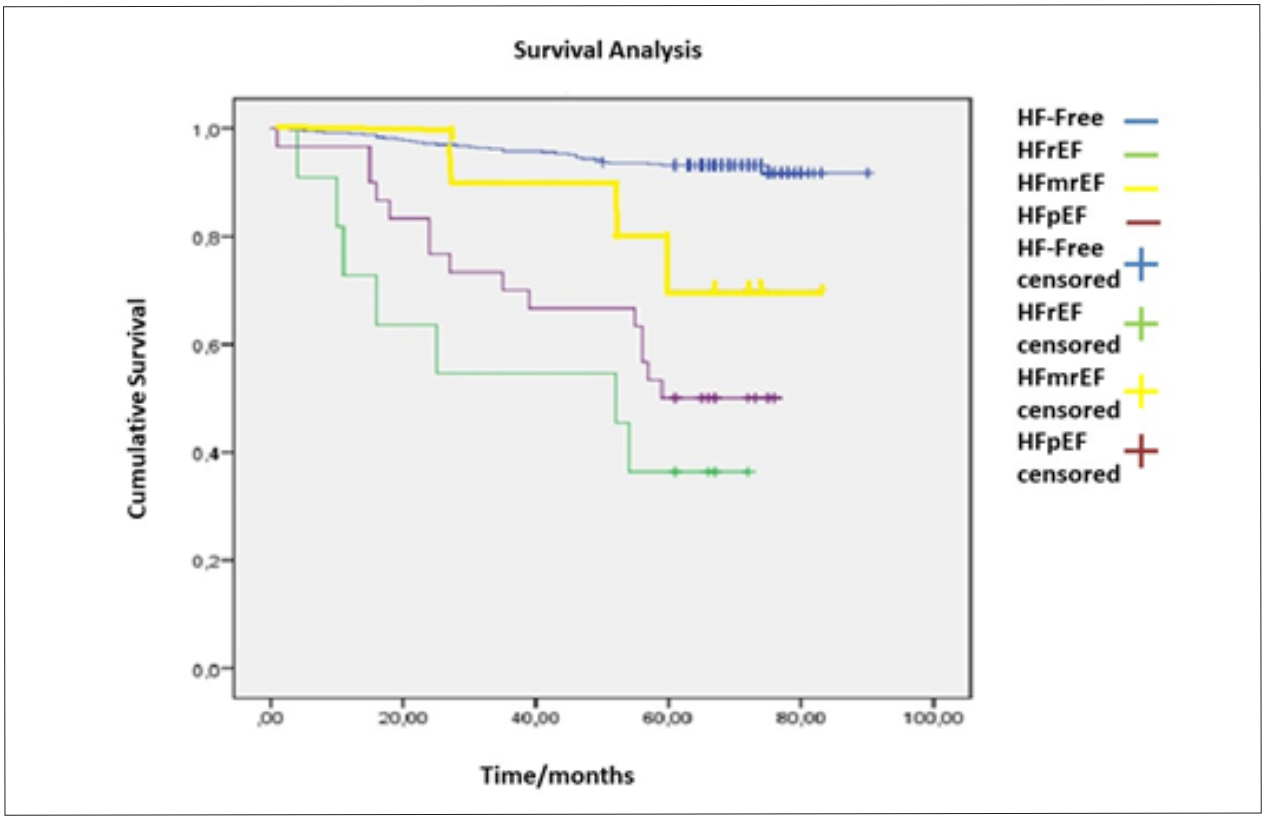


Figure 2 – *Kaplan-Meier curve showing that patients with HFmrEF had a worse composite outcome of all-cause death and cardiovascular hospitalization than patients without HF (p < 0.007), but patients with HFmrEF had better prognosis compared to patients with HFpEF and HFrEF (p < 0.001). HFrEF had the worst prognosis of the three phenotypes of HF. HF: heart failure; HFmrEF: HF with mid-range ejection fraction; HFpEF: HF with preserved ejection fraction; HFrEF: HF with reduced ejection fraction.*

Regarding prognosis, our study concluded that patients with HFmrEF had a better composite outcome of all-cause mortality and cardiovascular hospitalization than those with HFrEF and HFpEF (p < 0.001). Our results are in agreement with a meta-analysis by Altaie et al.[9] that showed that the HFmrEF phenotype had a significantly lower all-cause death rate than the HFrEF (RR, 0.9; 95% CI, 0.85 to 0.94; p < 0.001). However, differently from the present study, they found no significant difference between the all-cause mortality of HFpEF and HFmrEF (RR, 0.98; 95% CI, 0.86

Table 3 – Mean and confidence interval of survival probabilities in heart failure phenotypes

		Confidence interval 95%	
Variables	Means estimate	Lower limit	Upper limit
No HF	85.74	84.357	87.134
HFrEF	41.81	25.646	57.990
HFmrEF	72.00	60.544	83.456
HFpEF	54.56	45.561	63.572

HF: heart failure; HFmrEF: HF with mid-range ejection fraction; HFpEF: HF with preserved ejection fraction; HFrEF: HF with reduced ejection fraction.

to 1.12; p = 0.82).[9] Analyzing hospitalization due to HF in the meta-analysis by Altaie et al., they found no significant differences between HFrEF and HFmrEF (RR, 0.92; 95% CI, 0.84 to 1.01; p = 0.08) or between HFpEF and HFmrEF (RR, 1.05; 95% CI, 0.83 to 1.33; p = 0.69).

Further studies that investigate the prognosis and characterize HFmrEF with a larger sample are necessary. In addition, the present study paves the way for future randomized trials that investigate specific treatments for patients with HFmrEF.

Limitations

The results should be interpreted with several limitations. First, a small number of patients with HF were evaluated, which may not represent the whole population. Second, clinical evaluation and laboratory and echocardiographic variables, including LVEF, were based on a single measurement. Furthermore, although the sociodemographic characteristics of the studied population are quite similar to other urban areas worldwide, extrapolations of these results should be taken with caution. Lastly, since the study population comprised volunteers, it is possible that some selection bias was introduced, such as higher percentage of women.

Conclusion

The prevalence of ICFEI was similar to that observed in previous studies. The present study demonstrated that ICFEi has clinical and echocardiographic characteristics that are more similar to ICFEp than to ICFEr. In addition, our data show that ICFEi had a better prognosis compared to the other two phenotypes.

Author Contributions

Conception and design of the research: Jorge AJL, Barbetta LMS, Correia ETO, Rosa MLG, Mesquita ET; Acquisition of data: Jorge AJL, Leite AR, Saad MAN, Correia DM, Chermont S; Analysis and interpretation of the data: Jorge AJL, Martins WA, Rosa MLG; Statistical analysis: Rosa MLG, Santos CC; Writing of the manuscript: Jorge AJL, Barbetta LMS, Correia ETO; Critical revision of the manuscript for intellectual contente: Jorge AJL, Martins WA, Mesquita ET, Santos MMS.

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. Wang TJ, Evans JC, Benjamin EJ, Levy D, LeRoy EC, Vasan RS. Natural history of asymptomatic left ventricular systolic dysfunction in the community. Circulation. 2003;108(8):977-82.
2. McMurray JJV, 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: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012; 14(8):803-69.
3. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013;62(16):e147–239.
4. 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
5. Comitê Coordenador da Diretriz de Insuficiência Cardíaca. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda.Sociedade Brasileira de Cardiologia. Arq Bras Cardiol. 2018; 111(3):436-539.
6. Kapoor JR, Kapoor R, Ju C, Heidenreich PA, Eapen ZJ, Hernandez AF et al. Precipitating clinical factors, heart failure characterization, and outcomes in patients hospitalized with heart failure with reduced, borderline, and preserved ejection fraction. J Am Coll Cardiol HF 2016;4(6):464-72.
7. Tsuji K, Sakata Y, Nochioka K, Miura M, Yamauchi T, Onose T et al. Characterization of heart failure patients with midrange left ventricular ejection fraction-a report from the CHART-2 study. Eur J Heart Fail. 2017;19(10):1258-69.

8. Lauritsen J, Gustafsson F, Abdulla J. Characteristics and long-term prognosis of patients with heart failure and mid-range ejection fraction compared with reduced and preserved ejection fraction: A systematic review and meta-analysis. ESC Heart Fail 2018; 5(4): 685-94.

9. Altaie S, Khalife W. The prognosis of mid-range ejection fraction heart failure: a systematic review and meta-analysis. ESC Heart Fail. 2018;5(6):1008-16

10. Jorge AJL, Rosa MLG, Fernandes LCM, Freire MDC, Rodrigues RC, Correia DM da S, et al. Estudo da prevalência de insuficiência cardíaca em indivíduos cadastrados no Programa Médico de Família - Niterói. Estudo Digitalis: desenho e método. Rev Bras Cardiol. 2011;24;320–5.

11. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T,et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2016;29(4):277-314.

12. Rickenbacher P, Kaufmann BA, Maeder MT Bernheim A, Goetschalckx K, Pfister O, et al. Heart failure with mid-range ejection fraction: a distinct clinical entity? Insights from the Trial of Intensified versus standard Medical therapy in Elderly patients with Congestive Heart Failure (TIME-CHF). Eur J Heart Fail. 2017; 19:1586-1596.

13. Koh AS, Tay WT, Teng TH, Vedin O, Benson L, Dahlstrom U, et al. A comprehensive population-based characterization of heart failure with mid-range ejection fraction. Eur J Heart Fail. 2017;19(12):1624-34.

14. Solomon SD, Claggett B, Lewis EF, Desai A, Anand I, Sweitzer NK, et al. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J 2016;37(5):455–62.

15. Lund LH, Claggett B, Liu J, Lam CS, Jhund PS, Rosano GM, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail. 2018;20(8):1230–9.

16. Rastogi A, Novak E, Platts AE, Mann DL. Epidemiology, pathophysiology and clinical outcomes for heart failure patients with a mid-range ejection fraction. Eur J Heart Fail. 2017;19(12):1597-605.

Heart Failure with Mid-Range Ejection Fraction – A Temporary Condition or a Specific Group?

Eduardo Arrais Rocha,[1,2] Camila Pinto Cavalcante Miná,[3] Maria Eduarda Quidute Arrais Rocha[4]

Faculdade de Medicina da Universidade Federal do Ceará,[1] Fortaleza, CE - Brazil

Centro de Arritmia do Ceará,[2] Fortaleza, CE - Brazil

Hospital de Messejana Dr. Carlos Alberto Studart Gomes,[3] Fortaleza, CE - Brazil

Universidade de Fortaleza Centro de Ciências da Saúde,[4] Fortaleza, CE - Brazil

Short Editorial related to the article: Characteristics and Temporal Trends in the Mortality of Different Heart Failure Phenotypes in Primary Care

The latest epidemiological report from the American Heart Association indicates that 6.2 million Americans over 20 years of age had heart failure (HF), with the projection that this number could reach 8 million by 2030.[1] In Brazil, between 2008 and 2017, HF was the leading cardiovascular cause of hospitalization, accounting for 2.25% of all hospitalizations, with mortality of 14/100,000.[2] According to Fernandes et al., this rate reaches 19.2/100,000 in less developed states of Brazil.[2]

Faced with the prevalence of the severity of this disease, the study "Characteristics and temporal trends in the mortality of different heart failure phenotypes in primary care" has brought valuable data to better understand, stratify, and treat patients with HF.[3].

As described in the last decade, heart failure with mid-range ejection fraction (HFmrEF) has occupied a "grey zone," in patients with ejection fraction (EF) between 41% and 49%, comprising approximately 7% to 25% of all patients with HF. It is a group with heterogeneous characteristics. At times, it shows similarities with the group of patients with HF with reduced EF (HFrEF); at other times, with the group with HF with preserved EF (HFpEF), and sometimes it presents as a unique phenotype.[4] Some authors even argue that it is not a separate group, but rather a transition phenotype between HFrEF and HFpEF.[5]

In the study by Jorge et al.[3], the prevalence of the HFmrEF phenotype observed in a primary care service was 22%, close to that found in another Brazilian study, by Cavalcanti et al.,[6] where 26% of patients with acute HF presented the mid-range phenotype.[6] These frequencies are higher than those described in the study by Peterson et al.,[7] where 17% of patients treated for acute HF had HFmrEF.[7]

It is worth mentioning that, within this new category of HF, the literature suggests subgroups with different prognoses based on the analysis of the dynamic behavior of EF, as follows: impaired HFmrEF, recovered HFmrEF, and unchanged HFmrEF.[8] The study by Savarese et al.[9] evaluated 4,942 patients from the Swedish Heart Failure Registry who had at least 2 consecutive echocardiogram measurements with an average interval of 1.4 years. They analyzed the incidence of transition between phenotypic groups as increased EF, decreased EF, or stable EF, in addition to the prognostic implications of these changes. The authors observed the following results: of patients with HFpEF, 21% transitioned to HFmrEF, and 18% transitioned to HFrEF; of those with HFmrEF, 37% transitioned to HFrEF, and 25% transitioned to HFpEF; of patients with HFrEF, 16% transitioned to HFmrEF, and 10% transitioned to HFpEF. Patients who improved from HFrEF, transitioning to the HFmrEF or HFpEF phenotype had less mortality and hospitalization, and the outcome was the opposite for patients with HFpEF or HFmrEF who transitioned to the HFrEF phenotype.[9]

The description of the possibility of these 3 subgroups may explain the differences in results between different studies. If, in a given study, a subgroup with reduced EF in recovery predominated, they could possibly have characteristics that were more similar to those of the group with preserved EF. In another case, if there was a predominance of the HFmrEF subgroup that originally had better EF, but evolved with a gradual worsening, the characteristics could be more similar to the HFrEF group. It is also important to consider that the usual echocardiographic calculations of EF carried out in these studies have limitations and dynamic results that depend on the patients' hemodynamic conditions, and they have inter- and intra-observer variability. To resolve these limitations, new techniques such as strain are being incorporated.[10]

The article that gave rise to this editorial, a pioneer in the study of HFmrEF in Brazil, followed adequate methodology, and it brought diverse pieces of information that will certainly assist our clinical approaches. However, it is necessary to analyze the data in the context where the population was inserted, namely, in primary care, which may differ from global analysis of this subgroup.

There are some limitations to the interpretation of the results found, including the following: small cohort size, given the high prevalence of the disease, with only 51 diagnoses in 560 patients; all clinical, laboratory, and echocardiographic evaluations were performed at a single moment, and it was not possible to assess the evolution of these parameters over time; data on use of medication for HF were also collection at a single moment, and it was not possible to analyze whether the results reflected optimized medical treatment, considering the low rate of use of the main drugs at the time of the initial

Keywords

Heart Failure/physiopathology; Stroke Volume; Epidemiology; Hospitalization; Mortality

Mailing Address: Eduardo Arrais Rocha •
Faculdade de Medicina da Universidade Federal do Ceará - Cardiologia
Rua Capitão Francisco Pedro, 1290. Postal Code 60430-160, Fortaleza, CE – Brazil
E-mail: eduardoa@cardiol.br

DOI: https://doi.org/10.36660/abc.20210482

analysis of the study; and the lack of adequate characterization of the degrees of diastolic dysfunction.

There are some aspects that warrant attention in the characteristics of the groups. It was observed that half of the patients with HFmrEF were on diuretics; this was similar to the group with HFpEF and higher than the group with HFrEF. Another piece of data was in relation to the dosage of BNP, which was lower in the HFmrEF group than in the HFpEF group. These conflicting findings could influence the combined outcome that involved hospital admissions, reducing the difference between groups.

The low rate of use of beta-blockers in the group with HFrEF, with only 36% and 30% in the other groups, is rather concerning, in addition to the 60% to 70% rate of ACEi/ARB use. Is standard treatment for HF not being fulfilled in primary care units? Or did the groups become aware of the pathologies upon being included in the study, with these percentages reflecting an initial analysis? Both situations give rise to discussions regarding the need to actively search for these patients and to implement effective measures in order to guarantee the full application of standard therapies in the treatment of HF.

In light of these observations, the findings of this study need to be confirmed on the national level in larger analyses, not only in primary care groups, so that we may understand how our patients are really being managed, whether in accordance with broader scientific evidence, especially in relation to groups with greater severity.

Therefore, I congratulate the research group for their initiative in bringing information relevant to the screening of HF phenotypes in primary care, within the context of this clinical entity which is so incident and prevalent and which has such a high morbidity and mortality rate, even considering the many known therapeutic resources.[11]

References

1. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, et al. Heart disease and stroke statistics – 2020 update: summary. Circulation.2020;141(9):e139-e596.
2. Fernandes ADF, Fernandes GC, Mazza MR, Knijnik LM, Fernandes GS, Vilela AT, et al. Insuficiência cardíaca no Brasil subdesenvolvido: análise de tendência de dez anos. Arq Bras Cardiol.2020;114(2):222-31.
3. Jorge AJL, Barbetta LMS, Correia ETO, Martins WA, Leite AR, Saad MAN, et al. Characteristics and Temporal Trends in the Mortality of Different Heart Failure Phenotypes in Primary Care. Arq Bras Cardiol. 2021; 117(2):300-306. doi: https://doi.org/10.36660/abc.20190912
4. Srivastava PK, Hsu JJ, Ziaeian B, Fonarow GC. Hear failure with mid-range ejection fraction. Curr Heart Fail Rep. 2020;12(1):1-8.
5. Martone R, Marchionni N, Cappelli F. Heart failure with mid-range ejection fraction: current evidence and uncertainties. Monaldi Archives for Chest Disease.2019;89(1):1024.
6. Cavalcanti GP, Sarteschi C, Gomes GES, Medeiros CA, Pimentel JHM, Lafayette AR, et al. Decompensated heart failure with mild-range ejection fraction: epidemiology and in-hospital mortality risk factors. Int J Cardiovasc Sci.2020;33(1):45-54.
7. Peterson LC, Danzmann LC, Bartholomay E, Bodanese LC, Donay BG, Magedanz AV, et al. Sobrevida em pacientes com insuficiência cardíaca aguda e fração de ejeção intermediária em um país em desenvolvimento – estudo de coorte no sul do Brasil. Arq Bras Cardiol.2021;116(1):14-23.
8. Mesquita AT, Barbetta LMS, Correia ETO. Insuficiência cardíaca com fração de ejeção intermediária – estado da arte. Arq Bras Cardiol.2019;112(6):784-90.
9. Savarese G, Vedin O, D'Amario D, Uijl A, Dahlström U, Rosano G, et al. Prevalence and prognostic implications of longitudinal ejection fraction change in heart failure. JACC Heart Failure.2019;7(4)306-17.
10. Branca L, Sbolli M, Metra M, Fudim M. Heart failure with mid-range ejection fraction: pro and cons of the new classification of heart failure by European Society of Cardiology guidelines. Esc Heart Failure.2020;7:381-99.
11. Marcondes-Braga FG, Moura LAZ, Issa VS, Vieira JL, Rohde LE, Simões MV, et al. Atualização de tópicos emergentes da diretriz de insuficiência cardíaca - 2021 Arq Bras Cardiol.2021;116(6):1174-212

Original Article

Physiological Responses to Maximal and Submaximal Walking in Patients with Symptomatic Peripheral Artery Disease

Marcel Chehuen,[1] Aluisio Andrade-Lima,[2] Natan Silva Junior,[1] Roberto Miyasato,[1] Rodrigo W. Alves de Souza,[1] Anthony Leicht,[3] Patricia Chakur Brum,[1] Edilamar M. Oliveira,[1] Nelson Wolosker,[4] Claudia Lucia de Moraes Forjaz[1]

Universidade de São Paulo - Escola de Educação Física e Esportes,[1] São Paulo, SP - Brazil
Universidade Federal de Sergipe,[2] Aracaju, SE - Brazil
James Cook University,[3] Townsville, Queensland - Australia
Hospital Israelita Albert Einstein,[4] São Paulo, SP - Brazil

Abstract

Background: **Although maximal and submaximal walking are recommended for patients with peripheral artery disease (PAD), performing these exercises may induce different physiological responses.**

Objectives: **To compare the acute effects of maximal and submaximal walking on post-exercise cardiovascular function, regulation, and associated pathophysiological processes in patients with symptomatic PAD.**

Methods: **Thirty male patients underwent 2 sessions: maximal walking (Gardner's protocol) and submaximal walking (15 bouts of 2 minutes of walking separated by 2 minutes of upright rest). In each session, blood pressure (BP), heart rate (HR), cardiac autonomic modulation (HR variability), forearm and calf blood flows (BF), vasodilatory capacity (reactive hyperemia), nitric oxide (NO), oxidative stress (lipid peroxidation), and inflammation (four markers) were measured pre- and post-walking. ANOVAs were employed, and $p < 0.05$ was considered significant.**

Results: **Systolic and mean BP decreased after the submaximal session, but they increased after the maximal session (interactions, $p < 0.001$ for both). Diastolic BP did not change after the submaximal session ($p > 0.05$), and it increased after maximal walking (interaction, $p < 0.001$). HR, sympathovagal balance, and BF increased similarly after both sessions (moment, $p < 0.001$, $p = 0.04$, and $p < 0.001$, respectively), while vasodilatory capacity, NO, and oxidative stress remained unchanged ($p > 0.05$). Vascular and intercellular adhesion molecules increased similarly after both maximal and submaximal walking sessions (moment, $p = 0.001$).**

Conclusions: **In patients with symptomatic PAD, submaximal, but not maximal walking reduced post-exercise BP, while maximal walking maintained elevated cardiac overload during the recovery period. On the other hand, maximal and submaximal walking sessions similarly increased post-exercise HR, cardiac sympathovagal balance, and inflammation, while they did not change post-exercise NO bioavailability and oxidative stress.**

Keywords: **Walking; Peripheral Arterial Disease; Walking Speed; Hemodynamic Monitoring; Intermittent Claudication; Oxidative Stress; Byomarkers.**

Introduction

Peripheral artery disease (PAD) is characterized by the narrowing of the lower limb arteries, conventionally due to atherosclerosis.[1,2]{Norgren, 2007, Inter-society consensus for the management of peripheral arterial disease} Patients at the second stage of the disease (Fontaine classification) present a symptom known as intermittent claudication (IC), which is characterized by the appearance of pain in the lower leg during walking that is relieved with rest.[1,2] Additionally, patients with symptomatic PAD could present high blood pressure (BP) values,[3] cardiovascular overload,[3,4] cardiac autonomic dysfunction,[4] endothelial dysfunction, exacerbated oxidative stress, and inflammation.[5-7] All these physiological manifestations contribute to the progression of the disease and cardiovascular morbimortality.[2,3,6]

Exercise training has been considered the best treatment for patients with IC.[1,2] Regular training improves these patients' walking capacity, claudication symptoms, quality of life, and cardiovascular health.[1,8,9] Among the different training modalities, walking has been widely recommended by several guidelines.[1,2,9] However, the chronic effects of training are thought to result from the sum of acute bout responses,[10] which reinforces the importance of performing daily walking sessions to

Mailing Address: Aluisio Andrade-Lima •
Universidade Federal de Sergipe - Rua João Geniton da Costa, 306. Postal Code 49095-796, Aracaju, SE – Brazil
E-mail: aluisiolima@live.com
Manuscript received February 27, 2020, revised manuscript June 25, 2020, accepted August 12, 2020

DOI: https://doi.org/10.36660/abc.20200156

optimize chronic adaptations. However, acutely, each walking session may transiently increase cardiovascular risk.[10] Indeed, previous studies have reported that walking to near-maximal IC symptoms increases cardiac overload, endothelial dysfunction, oxidative stress, and inflammation,[7,11-13] which enhances the risk for ischemia and arrhythmias in predisposed patients.[14]

Accordingly, maximal walking may have hazardous post-exercise effects in patients with symptomatic PAD, and submaximal walking (until moderate leg pain) appears as a potential option that may promote lower post-exercise cardiac overload accompanied by moderate oxidative stress and inflammation. Novakovic et al.[15] have shown that walking at moderate pain improved several outcomes in these patients, such as vascular function. Additionally, previous studies have tested a specific submaximal walking protocol (15 bouts of 2 minutes of walking at pain threshold) and reported that it induces tolerable levels of leg pain and moderate metabolic and cardiovascular stimuli during its execution,[16] induces post-exercise hypotension,[17] and improves walking capacity and cardiovascular parameters after a period of regular training.[8]

Thus, the aim of this study was to compare, in patients with symptomatic PAD, the acute effects of maximal and submaximal walking exercises on the following post-exercise variables: i) cardiovascular function, assessed by BP, heart rate (HR) and rate-pressure product (RPP); ii) cardiac autonomic modulation, assessed by low (LF) and high-frequency (HF) components of HR variability and LF/HF ratio; iii) vascular function, assessed by forearm and calf blood flows (BF) and BF responses to reactive hyperemia; iv) endothelial function, assessed by nitric oxide (NO) bioavailability; v) oxidative stress, assessed by lipid peroxidation; and vi) inflammation, assessed by C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), vascular cell adhesion protein (VCAM) , and intercellular adhesion molecule (ICAM). The following were hypothesized: i) a maximal walking session would increase post-exercise cardiac overload (BP, HR, and RPP), sympathovagal balance (LF and LF/HF ratio), and vascular dysfunction, while the submaximal walking session would decrease BP and RPP, while inducing a lower increase on HR and sympathovagal balance; and ii) maximal and submaximal walking sessions would increase post-exercise oxidative stress and inflammation with greater responses after maximal walking.

Methods

This single center study followed a non-random repeated measurement design in which each patient underwent two experimental sessions conducted in a fixed order. The study protocol followed the Declaration of Helsinki. It was registered at the Brazilian Clinical Trials website (http://www.ensaiosclinicos.gov.br, RBR-3pq58k) and was approved by the Joint Committee on Ethics of Human Research of the School of Physical Education and Sport at the University of São Paulo (process 667.382). Written informed consent was obtained from all participants.

Participants

Patients were recruited from those assisted at the Vascular Unit of the Hospital das Clínicas of the University of São Paulo, Brazil, according to the possibility of contacting them. Male patients previously diagnosed with PAD and IC were invited. Inclusion criteria were the following: a) age ≥ 50 years; b) ankle-brachial index ≤ 0.90 in at least one leg[1]; c) Fontaine stage II (a and b) of PAD[1]; d) body mass index < 35 kg/m^2; e) resting systolic BP < 160 mmHg and diastolic BP < 105 mmHg; f) not currently taking β-blockers or non-dihydropyridine calcium channel blockers; g) ability to walk at least 2 minutes at 3.2 km/h on a treadmill; h) ability to undertake an incremental treadmill test limited by symptoms of IC; and i) absence of myocardial ischemia or complex arrhythmias during a treadmill test.

Preliminary evaluations

All patients underwent preliminary evaluation to identify whether they met the study criteria. They were interviewed to assess the following: age, presence of cardiovascular disease, risk factors, comorbid conditions, and current medication. Ankle-brachial index was measured as previously described.[1] Body mass and height were assessed with standard equipment (Welmy 110, Brazil), and body mass index was calculated. Resting brachial BP was measured by the auscultatory method after 5 minutes of seated rest. Three measurements were taken in each of 2 visits, and the mean value was calculated for each arm. The highest mean value was also documented. Finally, all patients undertook an exercise test on a treadmill following Gardner's protocol (3.2 km/h with 2% increase in grade per minute)[18] until maximal claudication pain was experienced. This test was also employed as a familiarization to the maximal effort.

Experimental protocol

Following the preliminary procedures, patients who fulfilled all study criteria underwent the experimental protocol that consisted of both experimental sessions, maximal and submaximal walking. The submaximal walking session was performed after the maximal session with an interval of at least 7 days between sessions. Moreover, all patients underwent 2 familiarization sessions before undergoing the submaximal session. During each session, cardiovascular, autonomic, endothelial, oxidative stress, and inflammatory variables were evaluated prior to and after the submaximal or maximal walking protocols.

Before both sessions, the patients were instructed to maintain similar routines for the prior 24 hours. In addition, they were instructed to avoid physical exercise for the previous 48 hours, alcoholic beverages for the previous 24 hours, and smoking on the day of the sessions. They were also instructed to take their medication regularly and to attend to the laboratory in a fasted state.

The sessions were conducted in a temperature-controlled laboratory (20 to 22 °C). Patients arrived at 7 am and received a standardized meal (two cereal bars and 50 ml of juice).[19,20] A catheter was then inserted into the antecubital vein of the left arm and kept patent by sterile saline. The patients then rested in the supine position for 20 minutes until the commencement of the experimental procedures.

Experimental procedures were initiated at 8 am with pre-exercise assessments performed in the supine position after a

10-minute stabilization period. Electrocardiogram (ECG) and respiration were recorded between 10 and 20 minutes to assess cardiac autonomic modulation. Auscultatory BP and HR were measured in triplicate between 20 and 25 minutes, and the mean value was used for analysis. A venous blood sample was then collected followed by the assessment of lower and upper limb BF and vasodilatory responses to reactive hyperaemia.

Subsequently, patients performed the walking exercise on a treadmill. In the maximal session, they walked at 3.2 km/h with grade increased 2% every minute until maximal pain (Gardner's protocol).[18] During the submaximal session, they performed 15 bouts of 2 minutes of walking separated by 2 minutes of upright rest, as previously described.[8,16,17] Treadmill speed was maintained at 3.2 km/h with the grade adjusted to maintain the HR of the pain threshold (i.e. the HR measured when the patients had experienced initial claudication pain during the preliminary maximal walking test).

At the end of the walking sessions, the patients immediately returned to supine position for the post-exercise assessments that included an immediate blood sampling. At 20 to 30 minutes of recovery, ECG and breathing movements were recorded for cardiac autonomic modulation assessment, followed by the assessments of auscultatory BP and HR in triplicate. Finally BF and vasodilatory responses were recorded.

Measurements

Cardiovascular function

Recordings of ECG were obtained at D2 (EMG System, Brazil) with HR determined by the ECG. Respiratory signal was obtained by a piezoelectric belt (UFI, Pneumotrace2, USA) positioned at the patients' thorax. Auscultatory BP was measured in the dominant arm using a mercury sphygmomanometer (Unitec, Brazil), and mean BP was calculated. RPP was calculated by the product of HR and systolic BP as a marker of myocardial oxygen consumption and, thus, of cardiac overload.[21]

Cardiac autonomic modulation

For cardiac autonomic evaluation, R-R intervals from the ECG and respiratory signals from the thoracic belt were inputted into a data acquisition system (WinDaq, DI-720, Akron, USA) at a sampling rate of 500 Hz/channel. Stationary segments of 250 to 300 beats were analyzed via spectral analysis of HR variability using the autoregressive method (Heart Scope, version 1.3.0.1, AMPS-LLC, USA). LF (LF_{RR}, 0.04 – 0.15 Hz) and HF (HF_{RR}, 0.15 – 0.4 Hz) components of HR variability were calculated and expressed in normalized units (nu). The LF/HF ratio was also calculated. All procedures followed the Task Force for HR variability.[22]

Vascular function

BF were simultaneously determined in the dominant forearm and the leg with the lowest ankle-brachial index, via venous occlusion plethysmography (Hokanson, AI6, USA).[23] Briefly, BF to the hand and the foot were interrupted by cuffs inflated to 200 mmHg positioned, respectively, around the wrist and the ankle. Other cuffs placed at the arm and the thigh were rapidly inflated for 10 seconds at 40 to 60 mmHg, followed by 10 seconds of deflation. Increases in forearm and calf volumes were detected by mercury strain gauges positioned at the largest circumference of these limb segments and recorded by specialized software (NIVP3; Hokanson, USA). Measurements were taken for 4 minutes (twelve 20-second cycles) and the first 2 and the last cycle measurement were excluded from analysis (i.e. mean of 9 cycles). Forearm and calf vasodilatory responses to reactive hyperemia were assessed immediately after determination of BF.[23] For this, BF to each limb was occluded for 5 minutes by inflating the thigh and forearm cuffs to 200 mmHg. Afterwards, the cuffs were released and post-occlusion BF were measured for 4 minutes as previously described. Vasodilatory response was calculated as the difference in the area under the curve (AUCBF) of the post- and pre-hyperemia BF measurements.

Blood analysis

In each sampling moment, 15 ml of blood were collected in standard anticoagulant EDTA-treated vacutainer tubes. Samples were centrifuged within 30 minutes, divided into aliquots and stored at –80 °C until analysis. Plasma concentrations of CRP, TNF-α, VCAM, and ICAM were determined by enzyme-linked immune-sorbent assays (ELISA) according to the manufacturer's instructions in each kit (Cayman Chemical, USA for CRP; and R&D Systems, USA for TNF-α, VCAM, and ICAM). Lipid peroxidation was analyzed by specific kits (Cayman Chemical, USA), and NO was analyzed by the chemiluminescence method with a specific analyzer (Sievers ® Nitric Oxide Analyzer NOA 280, USA).

Statistical analyses

Considering a power of 90%, an alpha error of 5%, and a standard deviation of 3 mmHg for systolic BP and 0.6 ml.100 ml $tissue^{-1}.min^{-1}$ for BF (i.e. the main clinical outcomes), the minimal sample sizes necessary to detect a difference of 4 mmHg in systolic BP and 0.5 ml.100 ml $tissue^{-1}.min^{-1}$ in BF were calculated to be 10 and 14 subjects, respectively. As other variables with greater variation were included in the study, the sample size used was greater.

Normality and homogeneity of variance for all data were checked using the Shapiro-Wilk and Levene tests, respectively. When non-normality of data was identified, a logarithmic transformation was applied, and normal distribution was obtained. Responses to walking sessions were compared by two-way ANOVA (Statsoft, Statistic for Windows 4.3, Oklahoma, USA) for repeated measures with session (maximal versus submaximal) and moment (pre- versus post-exercise) as the main factors. When pre-exercise values were significantly different between the sessions (i.e. for HR and RPP), an analysis of covariance (ANCOVA) was employed using the pre-exercise value as a covariate. The Newman-Keuls post-hoc test was used to identify significances when appropriate. $P < 0.05$ was considered significant, and data were presented as mean ± standard deviation for continuous variables and as frequency of appearance (%) for categorical variables, such as comorbidities and medication use.

Results

Fifty patients volunteered for the study, and 11 refrained from participating due to lack of time. Thus, 39 patients signed the informed consent and performed the preliminary examinations, 9 of which were excluded (5 due to ECG abnormalities in the exercise test and 4 due to interruption of exercise test for reasons other than claudication pain). Therefore, 30 patients underwent both the maximal and submaximal experimental sessions and their characteristics are shown in Table 1.

Hemodynamic and autonomic responses are shown in Table 2. Systolic and mean BP decreased after the submaximal session and increased after the maximal session (interactions, $p < 0.001$ for both). Diastolic BP increased only after maximal walking (interaction, $p < 0.001$). Pre-exercise HR and RPP were significantly higher in the submaximal session than the maximal walking one, and ANCOVA revealed that these pre-exercise differences did not affect the results. Thus, HR displayed similar increases after both the maximal and the submaximal walking bouts (moment, $p < 0.001$), while RPP increased significantly only after maximal walking (interaction, $p = 0.007$).

HF decreased while LF and the LF/HF ratio increased significantly and similarly after both the maximal and the submaximal walking sessions (moment, $p = 0.02$, $p = 0.05$, and $p = 0.04$, respectively).

Forearm and calf BF increased significantly and similarly after the maximal and the submaximal walking bouts (moment, $p < 0.001$), while forearm and calf vascular resistance decreased similarly after both walking bouts (moment, $p < 0.001$ and $p = 0.01$, respectively), and forearm and calf AUCBF did not change after either submaximal or maximal walking bouts (all $p > 0.05$).

Blood responses are shown in Table 3. NO, lipid peroxidation, CRP, and TNF-α did not change after either submaximal or maximal walking bouts (all $p > 0.05$), while ICAM and VCAM displayed a similar and significant increase after the maximal and the submaximal walking sessions (moment, $p = 0.001$ for both).

Discussion

The main findings of this study were that patients with symptomatic PAD presented the following: 1) a reduction in systolic BP after submaximal walking, as well as an increase in systolic BP after maximal walking; 2) an increase in RPP only after the maximal walking; 3) similar increases in HR, LF/HF ratio, LF, ICAM, and VCAM levels after the maximal and submaximal walking sessions; and 4) no changes in NO and vasodilatory capacity after either maximal or submaximal walking sessions.

Walking to submaximal, but not maximal pain decreased post-exercise BP. Previous studies[17,24] have already reported the occurrence of post-exercise hypotension (PEH, i.e., a decrease in BP after an exercise bout in comparison to pre-exercise values)[25,26] in patients with symptomatic PAD after walking

Table 1 – Patient characteristics

	Mean ± standard deviation
Age (years)	66 ± 11
Body mass index (kg/m²)	25.3 ± 3.2
Diagnosis of PAD	
ABI at rest	0.62 ± 0.12
COD (m)	218 ± 87
TWD (m)	606 ± 275
Comorbidities	
Obesity (%)	10.0
Hypertension (%)	73.3
Diabetes mellitus (%)	26.7
Dyslipidemia (%)	93.3
Current smokers (%)	33.3
Heart disease/stroke (%)	23.3
Drug therapy	
Aspirin (%)	93.3
Statin (%)	93.3
Antihypertensive agent (%)	60.0
Oral hypoglycemic (%)	26.7

Data are mean ± standard deviation or percentage (%). ABI: ankle-brachial index; COD: claudication onset distance; PAD: peripheral artery disease; TWD: total walking distance. Obesity defined as body mass index ≥ 30 kg/m². Diabetes, hypertension, dyslipidemia, heart disease, and stroke defined by previous medical diagnosis.

Table 2 – Hemodynamic and autonomic variables measured pre- and post-exercise in the submaximal and maximal walking sessions

	Submaximal		Maximal				
	Pre	Post	Pre	Post	p session	p moment	p interaction
Systemic hemodynamics (N = 30)							
Systolic BP (mmHg)	132 ± 16	125 ± 15*#	134 ± 13	138 ± 17*	0.01	0.18	0.01
Diastolic BP (mmHg)	77 ± 9	76 ± 8#	78 ± 8	83 ± 9*	0.01	0.01	0.01
Mean BP (mmHg)	95 ± 10	92 ± 9*#	96 ± 9	101 ± 10*	0.01	0.05	0.01
HR (bpm)	64 ± 9#	67 ± 9*#	68 ± 9	71 ± 10*	0.01	0.01	0.70
RPP (bpm* mmHg)	8466 ± 1466#	8308 ± 1433#	9010 ± 1394	9762 ± 1671*	0.01	0.01	0.01
Autonomic modulation (n=22)							
LF (nu)	56 ± 22	64 ± 20*	51 ± 18	60 ± 21*	0.12	0.05	0.75
HF (nu)	40 ± 21	31 ± 19*	44 ± 17	34 ± 19*	0.19	0.02	0.88
LF/HF ratio	0.2 ± 0.5	0.4 ± 0.4*	0.1 ± 0.4	0.3 ± 0.5*	0.11	0.04	0.74
Local hemodynamics (n = 21)							
Forearm BF	1.42 ± 0.63	1.68 ± 0.68*	1.41 ± 0.59	1.65 ± 0.67*	0.70	0.01	0.59
Calf BF	12.0 ± 7.1	13.7 ± 7.0*	12.2 ± 7.8	14.4 ± 8.8*	0.11	0.01	0.57
Forearm VR	80.9 ± 34.8	67.2 ± 30.0*	83.9 ± 40.6	73.6 ± 34.1*	0.18	0.01	0.14
Calf VR	56.8 ± 30.2	40.4 ± 19.8*	63.9 ± 29.5	52.4 ± 26.5*	0.02	0.01	0.52
Forearm AUCBF	1085 ± 507	1299 ± 609	1294 ± 676	1218 ± 476	0.66	0.38	0.50
Calf AUCBF	1081 ± 606	1152 ± 603	999 ± 467	1270 ± 825	0.89	0.13	0.20

*Data are mean ± standard deviation. AUC: area under the curve; BF: blood flow; BP: blood pressure; HF: high frequency; HR: heart rate; LF: low frequency; nu: normalized units; RPP: rate-pressure product; VR: vascular resistance. Values for BF are ml.100 ml tissue-1.min-1. * = different from pre in the same session (p < 0.05); # = different from the maximal session at the same moment (p < 0.05). Analyses performed by two-way ANOVA.*

Table 3 – Plasma concentrations of nitric oxide, oxidative stress, and inflammatory variables measured pre- and post-exercise in the submaximal and the maximal walking sessions

	Submaximal		Maximal				
	Pre	Post	Pre	Post	p session	p moment	p interaction
NO (µM)	14.32±5.65	13.59±4.63	13.53±4.51	13.68±4.21	0.29	0.24	0.57
Oxidative stress							
LPO (µM)	18.81±14.69	19.29±15.34	18.71±17.06	20.55±19.01	0.81	0.44	0.77
Inflammation							
CRP (pg/ml)	1868±1435	1843±1485	1614±1651	1837±1586	0.41	0.13	0.45
TNF-α (pg/ml)	1.18±0.36	1.24±0.29	1.21±0.28	1.23±0.25	0.75	0.21	0.57
ICAM (ng/ml)	223±96	236±99*	218±92	244±100*	0.74	0.01	0.08
VCAM (ng/ml)	619±250	671±286*	592±237	650±247*	0.16	0.01	0.75

*Data are mean ± standard deviation. CRP: C-reactive protein; ICAM: intercellular adhesion molecule; LPO: lipid peroxidation; NO: nitric oxide; TNF-α: tumor necrosis factor-α; VCAM: vascular cell adhesion protein . * = different from pre in the same session (p < 0.05). Analyses performed by two-way ANOVA.*

to moderate pain. The novelty of this study was to provide evidence that, in patients with PAD at Fontaine stage II, PEH did not occur when walking was performed to maximal pain, and BP remained elevated after maximal walking. As PEH is known as a clinically relevant phenomenon in hypertensive populations,[27] submaximal, but not maximal walking may produce acute hypotensive benefits in patients with IC and hypertension. Moreover, recent evidence has shown that PEH correlates with decreases in BP after a training period, and it is a possible predictor of the chronic responsiveness.[28,29] Thus, these results raise the hypothesis that submaximal walking might produce better chronic hypotensive effects than maximal walking in this population. This needs to be tested by future studies.

Post-exercise HR increased similarly after the maximal and submaximal walking sessions, which is consistent with the similar increase observed in cardiac autonomic modulation changes towards sympathetic predominance after both

walking sessions (i.e. a similar increase in LF and the LF/HF ratio, as well as a decrease in HF).[30] This lack of difference between the maximal and submaximal sessions was, to a certain extent, unexpected, given that, in other populations, changes in post-exercise HR and sympathovagal modulation are usually associated with exercise intensity.[31] This apparently contradictory result may be explained by the fact that the submaximal walking session lasted longer (30 minutes, total distance walked = 1600 m) than the maximal session (12 ± 5 minutes, total distance walked = 606 ± 275 m). Thus, as pain produces sympathetic activation,[32] it is possible that, despite the moderate intensity, the longer period of pain in the submaximal session may have led to a sustained increase in sympathetic modulation and, consequently, HR during the recovery period, matching the increase produced by the more intense but shorter maximal session. Additionally, although post-exercise HR increased in both walking sessions, BP decreased only in the submaximal walking session, consequently leading to higher RPP after maximal walking, which reflects greater cardiac overload, and, consequently, greater risk of acute adverse events after maximal walking.[14] Thus, these results suggest that submaximal walking may be safer for patients predisposed to acute cardiovascular events.

Forearm and calf BF increased similarly after the submaximal and maximal walking sessions, and these responses are in agreement with previous studies.[17,33] However, interestingly, vasodilatory capacity did not change after either walking session, whereas previous studies reported decreased endothelial function after maximal walking.[12,34] Possible differences among the studies may be related to the methods used to assess vascular function (plethysmograph versus ultrasound). Nevertheless, in the current study, the absence of change in vasodilatory capacity is in accordance with the maintenance of NO and oxidative stress markers.

As expected, maximal and submaximal walking sessions increased inflammatory markers. However, different from the hypothesis, inflammation increased similarly after both sessions. Once again, this response may be related to the fact that exercise duration was longer in the submaximal walking session, leading to similar magnitude of inflammation, in spite of lower pain.

The absence of paired volume between the two walking sessions is a limitation to this study, which precludes us from attributing the results solely to the degree of pain. However, as a first study comparing post-exercise maximal and submaximal responses, this study opted to use a maximal protocol extensively investigated in literature[7,11,34] and a submaximal protocol, both of which have already been demonstrated to elicit cardiovascular benefits.[8,17] Future studies should compare other maximal and submaximal protocols with similar volume. Additionally, it is important to mention that this study was conducted with men at Fountain stage IIa and IIb, and post-walking responses may differ in women, in patients at other stages of the disease, and in patients with different clinical characteristics, notwithstanding Fontaine stage II. Future studies can overcome these limitations by studying women and other patients with PAD. In addition, measurements were performed only in one time-point during the post-exercise period. For a better understanding of responses, a follow-up for a longer period, with more measurements, should be performed in future investigations.

Conclusions

In male patients with symptomatic PAD, walking to submaximal, but not maximal pain reduces post-exercise BP, while only maximal walking elevates post-exercise RPP. On the other hand, maximal and submaximal walking sessions produce similar post-exercise increases in HR, cardiac sympathovagal balance, BF, and inflammation.

Practical implications

- Submaximal, but not maximal walking reduces BP in the post-exercise period.
- Only maximal walking increases post-exercise cardiac load.
- Submaximal and maximal walking similarly increase post-exercise inflammation.
- Submaximal walking might be more adequate than maximal walking for patients with symptomatic PAD, because it results in lower acute cardiovascular risk during the recovery period.

Author Contributions

Conception and design of the research: Chehuen M, Andrade-Lima A, Silva Junior N, Leicht A, Brum PC, Oliveira EM, Wolosker N, Forjaz CLM; Acquisition of data: Chehuen M, Andrade-Lima A, Silva Junior N, Miyasato R, Souza R; Analysis and interpretation of the data: Chehuen M, Andrade-Lima A, Silva Junior N, Miyasato R, Souza R, Leicht A, Brum PC, Oliveira EM, Wolosker N, Forjaz CLM; Statistical analysis: Chehuen M, Andrade-Lima A, Forjaz CLM; Obtaining financing: Forjaz CLM; Writing of the manuscript: Chehuen M, Andrade-Lima A, Leicht A, Brum PC, Oliveira EM, Wolosker N, Forjaz CLM; Critical revision of the manuscript for intellectual content: Chehuen M, Andrade-Lima A, Silva Junior N, Miyasato R, Souza R, Leicht A, Brum PC, Oliveira EM, Wolosker N, Forjaz CLM.

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 postdoctoral submitted by Marcel Chehuen, from Universidade de São Paulo.

References

1. Hirsch AT, Haskal ZJ, Hertzer NR, Bakal CW, Creager MA, Halperin JL, et al. ACC/AHA 2005 Practice Guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients With Peripheral Arterial Disease): endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation; National Heart, Lung, and Blood Institute; Society for Vascular Nursing; TransAtlantic Inter-Society Consensus; and Vascular Disease Foundation. Circulation. 2006;113(11):e463-654.

2. Norgren L, Hiatt WR, Dormandy JA, Nehler MR, Harris KA, Fowkes FG, et al. Inter-society consensus for the management of peripheral arterial disease. Int Angiol. 2007;26(2):81-157.

3. Bhatt DL, Steg PG, Ohman EM, Hirsch AT, Ikeda Y, Mas JL, et al. International prevalence, recognition, and treatment of cardiovascular risk factors in outpatients with atherothrombosis. JAMA. 2006;295(2):180-9.

4. Goernig M, Schroeder R, Roth T, Truebner S, Palutke I, Figulla HR, et al. Peripheral arterial disease alters heart rate variability in cardiovascular patients. Pacing Clin Electrophysiol. 2008;31(7):858-62.

5. Brevetti G, Giugliano G, Brevetti L, Hiatt WR. Inflammation in doença arterial periférica. Circulation. 2010;122(18):1862-75.

6. Chapman MJ. From pathophysiology to targeted therapy for atherothrombosis: a role for the combination of statin and aspirin in secondary prevention. Pharmacol Ther. 2007;113(1):184-96.

7. Signorelli SS, Mazzarino MC, Di Pino L, Malaponte G, Porto C, Pennisi G, et al. High circulating levels of cytokines (IL-6 and TNFalpha), adhesion molecules (VCAM-1 and ICAM-1) and selectins in patients with peripheral arterial disease at rest and after a treadmill test. Vasc Med. 2003;8(1):15-9.

8. Chehuen M, Cucato GG, Carvalho CRF, Ritti-Dias RM, Wolosker N, Leicht AS, et al. Walking training at the heart rate of pain threshold improves cardiovascular function and autonomic regulation in intermittent claudication: A randomized controlled trial. J Sci Med Sport. 2017;20(10):886-92.

9. Gerhard-Herman MD, Gornik HL, Barrett C, Barshes NR, Corriere MA, Drachman DE, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Doença arterial periférica: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2017;135(12):e686-e725.

10. Luttrell MJ, Halliwill JR. Recovery from exercise: vulnerable state, window of opportunity, or crystal ball? Front Physiol. 2015;6:204.

11. Palmer-Kazen U, Religa P, Wahlberg E. Exercise in patients with intermittent claudication elicits signs of inflammation and angiogenesis. Eur J Vasc Endovasc Surg. 2009;38(6):689-96.

12. Silvestro A, Scopacasa F, Oliva G, de Cristofaro T, Iuliano L, Brevetti G. Vitamin C prevents endothelial dysfunction induced by acute exercise in patients with intermittent claudication. Atherosclerosis. 2002;165(2):277-83.

13. Ritti-Dias RM, Meneses AL, Parker DE, Montgomery PS, Khurana A, Gardner AW. Cardiovascular responses to walking in patients with doença arterial periférica. Med Sci Sports Exerc. 2011;43(11):2017-23.

14. Svensson P, Niklasson U, Ostergren J. Episodes of ST-segment depression is related to changes in ambulatory blood pressure and heart rate in intermittent claudication. J Intern Med. 2001;250(5):398-405.

15. Novakovic M, Krevel B, Rajkovic U, Vizintin Cuderman T, Jansa Trontelj K, Fras Z, et al. Moderate-pain versus pain-free exercise, walking capacity, and cardiovascular health in patients with doença arterial periférica. J Vasc Surg. 2019;70(1):148-56.

16. Cucato GG, Chehuen Mda R, Costa LA, Ritti-Dias RM, Wolosker N, Saxton JM, et al. Exercise prescription using the heart of claudication pain onset in patients with intermittent claudication. Clinics (Sao Paulo). 2013;68(7):974-8.

17. Cucato GG, Chehuen Mda R, Ritti-Dias RM, Carvalho CR, Wolosker N, Saxton JM, et al. Post-walking exercise hypotension in patients with intermittent claudication. Med Sci Sports Exerc. 2015;47(3):460-7.

18. Gardner AW, Skinner JS, Cantwell BW, Smith LK. Progressive vs single-stage treadmill tests for evaluation of claudication. Med Sci Sports Exerc. 1991;23(4):402-8.

19. Hall WL, Vafeiadou K, Hallund J, Bugel S, Koebnick C, Reimann M, et al. Soy-isoflavone-enriched foods and inflammatory biomarkers of cardiovascular disease risk in postmenopausal women: interactions with genotype and equol production. Am J Clin Nutr. 2005;82(6):1260-8; quiz 365-6.

20. Smith TJ, Karl JP, Wilson MA, Whitney CC, Barrett A, Farhadi NF, et al. Glycaemic regulation, appetite and ex vivo oxidative stress in young adults following consumption of high-carbohydrate cereal bars fortified with polyphenol-rich berries. Br J Nutr. 2019;121(9):1026-38.

21. White WB. Heart rate and the rate-pressure product as determinants of cardiovascular risk in patients with hypertension. Am J Hypertens. 1999;12(2 Pt 2):50S-5S.

22. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J. 1996;17(3):354-81.

23. Thijssen DH, Bleeker MW, Smits P, Hopman MT. Reproducibility of blood flow and post-occlusive reactive hyperaemia as measured by venous occlusion plethysmography. Clin Sci (Lond). 2005;108(2):151-7.

24. Cavalcante BR, Ritti-Dias RM, Soares AH, Lima AH, Correia MA, De Matos LD, et al. A Single Bout of Arm-crank Exercise Promotes Positive Emotions and Post-Exercise Hypotension in Patients with Symptomatic Doença arterial periférica. Eur J Vasc Endovasc Surg. 2017;53(2):223-8.

25. de Brito LC, Fecchio RY, Pecanha T, Lima A, Halliwill J, Forjaz CLM. Recommendations in Post-exercise Hypotension: Concerns, Best Practices and Interpretation. Int J Sports Med. 2019;40(8):487-97.

26. Kenney MJ, Seals DR. Postexercise hypotension. Key features, mechanisms, and clinical significance. Hypertension. 1993;22(5):653-64.

27. 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.

28. Kiviniemi AM, Hautala AJ, Karjalainen JJ, Piira OP, Lepojarvi S, Ukkola O, et al. Acute post-exercise change in blood pressure and exercise training response in patients with coronary artery disease. Front Physiol. 2014;5:526.

29. Moreira SR, Cucato GG, Terra DF, Ritti-Dias RM. Acute blood pressure changes are related to chronic effects of resistance exercise in medicated hypertensives elderly women. Clin Physiol Funct Imaging. 2016;36(3):242-8.

30. de Brito LC, Rezende RA, da Silva Junior ND, Tinucci T, Casarini DE, Cipolla-Neto J, et al. Post-Exercise Hypotension and Its Mechanisms Differ after Morning and Evening Exercise: A Randomized Crossover Study. PLoS One. 2015;10(7):e0132458.

31. Cote AT, Bredin SS, Phillips AA, Koehle MS, Warburton DE. Greater autonomic modulation during post-exercise hypotension following high-intensity interval exercise in endurance-trained men and women. Eur J Appl Physiol. 2015;115(1):81-9.

32. Schlereth T, Birklein F. The sympathetic nervous system and pain. Neuromolecular Med. 2008;10(3):141-7.

33. da Silva ND, Jr., Roseguini BT, Chehuen M, Fernandes T, Mota GF, Martin PK, et al. Effects of oral N-acetylcysteine on walking capacity, leg reactive hyperemia, and inflammatory and angiogenic mediators in patients with intermittent claudication. Am J Physiol Heart Circ Physiol. 2015;309(5):H897-905.

34. Allen JD, Stabler T, Kenjale A, Ham KL, Robbins JL, Duscha BD, et al. Plasma nitrite flux predicts exercise performance in peripheral arterial disease after 3months of exercise training. Free Radic Biol Med. 2010;49(6):1138-44.

The Paradox of Exercise Intensity in Preventing Cardiovascular Events in Peripheral Arterial Occlusive Disease

Pablo de Souza[1,2] *and Cássio Perfete*[1]

Clínica Cardiosport,[1] *Florianópolis SC - Brazil*

Instituto de Cardiologia de Santa Catarina (ICSC),[2] *São José SC - Brazil*

Short Editorial related to the article: Physiological Responses to Maximal and Submaximal Walking in Patients with Symptomatic Peripheral Artery Disease

Peripheral arterial disease (PAD) is characterized by narrowing of the arteries of the lower limbs due to atherosclerotic involvement. Its clinical manifestations go far beyond just a reduction in blood flow, leading to chronic ischemia. Current evidence shows that endothelial dysfunction, oxidative stress, arterial stiffness and inflammation also lead to functional impairment, consequently to patient decline.[1]

All these factors end up impacting the quality of life of individuals, as it reduces their walking resistance, with intermittent claudication (IC) as the main symptom. Last but not least, we have also found progressive damage to muscle fibers caused by this chronic ischemia, further worsening the dysfunction of the skeletal muscle and metabolic morphology of the limb. This ends up creating an important barrier to the practice of physical activity, perpetuating and increasing the risk of cardiovascular events.[1-3]

To reduce these factors, the guidelines consider physical exercise as an essential tool in the therapeutic approach. Randomized controlled trials (RCT) demonstrate that although we did not obtain an improvement in the ankle-brachial index (ABI) with this approach, we were able to extend walking time, the maximum walking distance (MWD), neutralize IC, and therefore improve the quality of life. In 30 RCTs, including 1816 patients with IC, pain-free walking distance and MWD increased on average 82 and 109 meters, respectively, in up to two years.[4-9]

A meta-analysis of 25 randomized studies (1,054 patients) addressing exercise strategies in the rehabilitation of patients with PAD, found that supervised treadmill exercise was better than the control group, with a gain of 128 meters in pain-free walking distance and 180 meters at the maximum walking distance. In contrast, 3 RCTs (n=493) with PAD found that home walking exercises, when combined with behavior change techniques, improved the 6-minute walking test distance more than interventions on a supervised treadmill (45–54 meters vs. 33–35 meters, respectively). This fact, perhaps, may be due to the greater ease and applicability of exercises on the ground compared to the treadmill, which requires learning time.[5-8]

However, in addition to the benefits shown, it is also important to understand the risks inherent to the degree of intensity of physical exercise in this group of patients, since each session may acutely increase their cardiovascular risk temporarily. Previous studies have reported that walking with near-maximal IC symptoms promotes increased cardiac overload, endothelial dysfunction, oxidative stress, and inflammation.[6-9]

In this issue of Arquivos Brasileiros de Cardiologia, Marcel Chehuen et al. compared the acute physiological effects of post-exercise maximal and submaximal walking exercises in patients with symptomatic PAD. Of the 50 selected patients, only 30 were included in the study. The variables analyzed were: cardiovascular function, heart rate (HR) and its variability, autonomic modulation, vascular and endothelial function, oxidative stress and inflammation. It was possible to observe, regarding the acute effects, a reduction in systolic BP after the submaximal test, as opposed to the maximum session, which increased with statistical significance. Regarding diastolic BP, there was an increase only with the maximum walk ($p<0.001$) as well as the double product ($p=0.007$). Variables such as HR and inflammation (ICAM and VCAM) had similar increases with statistical significance for both tests. And when the variables of oxidative stress and endothelial function were analyzed, there were no changes in the values of nitric oxide and vasodilator capacity between the sessions, therefore without statistical significance.[10]

In fact, submaximal post-test hypotension had been reported in previous studies, but not for the maximal test, which even increased blood pressure in these patients. This could imply an additional therapy for hypertensive and PAD patients, using submaximal — not maximal — walking exercise to promote chronic hypotensive benefits in this population. Besides, its prescription would be more appropriate than maximal walking exercise, as it would result in a lower acute cardiovascular risk during the recovery period.

Although we found important and interesting results in this study, it only included men, in Fountain IIa/IIb stages, and cannot be extrapolated to women or to any other stages of the disease, as physiological responses could be different. Also worthy of note, this is a single-center study including a small number of participants. We still need larger randomized studies, including women and other stages of the disease, in order to overcome these limitations.[10]

Keywords

Coronary Artery Disease: Rehabilitation; Risk Factors; Intermittent Claudication; Exercise; Walking; Motor Activity.

Mailing Address: Pablo de Souza •
Rua Luiz Delfino, 146 – Ap. 102. Postal Code 88015-360, Centro, Florianópolis, SC – Brazil
E-mail: pablocardiologia@gmail.com

DOI: https://doi.org/10.36660/abc.20210595

References

1. Ismaeel A, Brumberg RS, Kirk JS, Papoutsi E, Farmer PJ, Bohannon WT, et al. Oxidative stress and arterial dysfunction in peripheral artery disease. Antioxidants(Basel). 2018;7(10):145.
2. Kim K, Anderson EM, Scali ST, Ryan T. Skeletal muscle mitochondrial dysfunction and oxidative stress in peripheral arterial disease: a A Unifying Mechanism and Therapeutic Target. Antioxidants. 2020;9(12):1304.
3. Correia MA, Cucato GG, Lanza,FC, Peixoto RAO, Zerati AE, Puech-Leão P, et al. Relationship between gait speed and physical function in patients with symptomatic peripheral artery disease. Clinics) São Paulo).2019;74:e1254.
4. Aboyans V, Ricco JB, Bartelink ML, Bjorck M, Brodmann M, Cohnert T, et al. 2017 –ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS):Document covering atherosclerotic, renal, upper and lower extremity arteries endorded by : the European Stroke Organization(ESO) The Task Force for the Diagnosis and Treatment of Peripheral Arterial Diseases of the European Society of Cardiology (ESC) ando f the European Society for Vascular Surgery (ESVS). Eur Heart JK, 2018;39(9):763-816.
5. McDermott MM. Exercise rehabilitation for peripheral artery disease: a review. J Cardiopulm Rehabil Prev. 2018; 38(2):63-9.
6. Signorelli SS, Marino E, Scuto S, Di Raimondo D. Pathphysiol of peripheral arterial disease (PAD): a review on oxidative disorders. Int J Mol Sci. 2020;21(12):4393.
7. Gerage AM, Correia MA, Oliveira PML, Palmeira AC, Domingues WJR. Zeratti AE,et al. Physical activitylevels in peripheral artery disease patients. Arq Bras Cardiol. 2019;113(3):410-6.
8. Farah BQ, Ritti-Dias RM, Montgomery P, Cucato GG, Gardner A. Exercise intensity during 6-minute walk test in patients with peripheral artery disease. Arq Bras Cardiol. 2020;114(3):486-92
9. Patelis N, Karaolanis G, Kouvelos GN, Hart C, Metheiken S. The effect of exercise on coagulation and fibrinolysis factors in patients with peripheral arterial disease. Exp Biol Med (Maywood). 2016;241(15):1699-707.
10. Chehuen M, Andrade-Lima A, Silva Junior N, Miyasato R, Souza RWA, Leicht A, et al. Physiological Responses to Maximal and Submaximal Walking in Patients with Symptomatic Peripheral Artery Disease. Arq Bras Cardiol. 2021; 117(2):309-316. doi: https://doi.org/10.36660/abc.20200156

In- and Out-of-Hospital Deaths by Acute Myocardial Infarction in Brazilian State Capitals

Sterffeson Lamare Lucena de Abreu,[1,2] Joana D'Arc Matos França de Abreu,[1,2] Maria dos Remédios Freitas Carvalho Branco,[2] Alcione Miranda dos Santos[2]

Hospital Universitário da Universidade Federal do Maranhão,[1] São Luís, MA - Brazil

Universidade Federal do Maranhão - Pós Graduação em Saúde Coletiva,[2] São Luís, MA - Brazil

Abstract

Background: **Acute myocardial infarction (AMI) is the main cause of death in Brazil and the world. Approximately half of these deaths occur outside the hospital.**

Objectives: **To analyze the distribution, temporal evolution, and sociodemographic characteristics (SDC) of in- and out-of-hospital deaths by AMI in Brazilian state capitals and their relationship with municipal development indicators (MDI).**

Methods: **This is an ecological study of the number of deaths due to AMI reported annually by the 27 Brazilian state capitals from 2007 to 2016; these were divided into 2 groups: in-hospital (H) and out-of-hospital (OH). We evaluated the temporal evolution of mortality rates in each group and differences in SDC. Negative binomial regression models were used to compare the temporal evolution of the number of deaths in each group with the following variables: residing in the South/Southeast regions (S/SE), municipal human development index (MHDI), Gini coefficient, and expected years of schooling (EYS). We considered p-values < 0.05 as statistically significant.**

Results: **The OH mortality rate increased with time for all state capitals. All studied SDC were different between groups (p < 0.001). In the OH group, most deaths were of men and patients aged 80 years or older and not married. S/SE increased the incidence of OH deaths (incidence rate ratio [IRR] = 2.84; 95% confidence interval [CI] = 1.67–4.85), while higher EYS reduced it (IRR = 0.86; 95% CI = 0.77–0.97). In the H group, higher MHDI reduced the incidence of deaths (IRR = 0.44; 95% CI = 0.33–0.58), while higher EYS increased it (IRR = 1.09; 95% CI = 1.03–1.15).**

Conclusions: **In- and out-of-hospital deaths due to AMI in Brazilian state capitals were influenced by MDI, presented sociodemographic differences and a progressive increase in out-of-hospital occurrences.**

Keywords: **Myocardial Infarction; Out-of-Hospital; Epidemiology; Deaths; Demographic Indicators; Social Indicators; Mortality; Death, Sudden Cardiac.**

Introduction

Acute myocardial infarction (AMI) is the main individual cause of death in Brazil and the world.[1,2] It has a mean mortality of 30% when untreated and of less than 6% when appropriate treatment is administered in time.[3] Half of these deaths occur within the first 2 hours of symptom onset and 80% happen in the first 24 hours, resulting in many deaths before any hospital care.[4]

Appropriate treatment of high-risk AMI is costly, and its availability is concentrated in large urban areas, mainly in state capitals; this is especially true in the North, Northeast, and Central-West regions of Brazil.[5] Although epidemiological studies have shown that mortality due to AMI is slowly decreasing worldwide, this reduction is smaller in countries with lower Gross Domestic Products (GDPs), lower social classes, and socioeconomically disadvantaged regions.[6-8]

Few studies have been published on out-of-hospital deaths due to AMI. Most of them consider general mortality without distinguishing between in-hospital and out-of-hospital deaths. Clinical studies on risk factors have been performed with patients who received hospital care. It is unknown whether deaths occurring out of the hospital environment presented sociodemographic differences in comparison with those who happened within a hospital, and the association of local and environmental factors with out-of-hospital mortality is still not well defined.[9,10]

The aim of this study was to temporally analyze in- and out-of-hospital deaths due to AMI in Brazilian state capitals, identifying sociodemographic differences and considering

Mailing Address: Sterffeson Lamare Lucena de Abreu •
Hospital Universitário da Universidade Federal do Maranhão Cardiologia - Rua Silva Jardim, 215. Postal Code 65020-560, Centro, São Luís, MA Brazil
E-mail: sterffeson@hotmail.com, sterffeson@cardiol.br
Manuscript received January 26, 2020, revised manuscript June 21, 2020, accepted August 12,2020

DOI: https://doi.org/10.36660/abc.20200043

municipal development indices. We chose to assess only the state capitals because all of them currently provide advanced treatment of AMI.[11]

Method

This is an ecological study of deaths due to AMI occurred in the 27 Brazilian state capitals between 2007 and 2016. Data on deaths per state capital (in- or out-of-hospital occurrence, sex, age group, schooling, marital status, and skin color) were obtained from the Mortality Information System (SIM), an online platform created by the informatics department of the Unified Health System (DATASUS) for regular retrieval of mortality data in Brazil. Deaths were divided into 2 groups according to the place of occurrence: in-hospital or out-of-hospital.

For selecting deaths due to AMI in the SIM, we considered entries that had AMI as the primary cause of death (International Classification of Diseases [ICD]-10: I21). Deaths with unknown place of occurrence were not included in this study.

In- and out-of-hospital mortality rates were obtained by calculating the rate between deaths due to AMI and the population of each state capital (per 100 000 inhabitants). These rates are presented as means, standard deviations (SDs), and minimum and maximum values.

To assess the temporal evolution of mortality rates in both groups, we calculated annual in- and out-of-hospital mortality rates for all Brazilian state capitals. The population was corrected by linear interpolation and extrapolation using data from demographic census of 2000, 2010, and the 2017 projection made by the Brazilian Institute of Geography and Statistics (IBGE). Rates were presented as deaths per 100 000 inhabitants and expressed as a line graph.

The Atlas Brasil platform of the United Nations Development Program (PNUD) was used for obtaining independent variables (municipal human development index [MHDI], Gini coefficient, and expected years of schooling), as well as information on the population of each state capital.[12]

Statistical analysis

For comparing the number of deaths in both groups according to sociodemographic characteristics (sex, age group, schooling, marital status, and skin color), we used the chi-squared test. Sociodemographic characteristics were presented as absolute and relative frequencies. To demonstrate the impact of each characteristic, we calculated the standardized residuals of chi-squared tests, which are presented as Z in Table 2. Considering a significance level of 5%, Z-values > +1.96 or < -1.96 were statistically significant and the plus and minus signs showed the direction of differences between groups.

To verify which independent variables were associated with the number of deaths in both groups, we used the panel data methodology, in which information from various sampling units (each state capital) was assessed through time, that is, observations were considered in 2 dimensions: the sampling unit and time.[13] Therefore, we used Poisson and negative binomial regression models with temporal adjustment and weighted by the population of each capital for each of the groups. Weighting was performed according to the population of each capital so that each sampling unit had the same weight when evaluating associations.

The models were tested with fixed and random effects. Those with fixed effects led to each capital having its own intercept, serving as its own control, which allowed the adjustment for unmeasured variables that did not change with time (such as census data, which are updated every 10 years).[13]

For choosing the model with the best fit, we considered the Akaike Information Criterion (AIC).[14] The lower the AIC, the better the fit. We also estimated the incidence rate ratio (IRR) and its respective confidence interval, considering as reference a 95% confidence interval (95% CI). Statistical analysis was performed using Stata software, version 14.0. This study only used data available in the public domain, thus not requiring assessment by a research and ethics committee as it does not fit the terms of Resolution 466, of December 2012.[15]

Results

Between 2007 and 2016, 189 634 deaths due to AMI were reported in Brazilian state capitals; 41.7% of them were out-of-hospital deaths. The mean mortality rate per 100 000 inhabitants in state capitals was 25.2 ± 1.3 for in-hospital deaths and 18 ± 1.2 for out-of-hospital deaths. The temporal evolution of the annual rate for all capitals in both groups is demonstrated in Figure 1.

The highest and lowest mean death rates were reported in Recife (43.2%) and Palmas (8.7%), respectively, for the in-hospital group, and in Rio de Janeiro (33.8%) and Macapá (4.7%) for the out-of-hospital group (Table 1). In many state capitals, out-of-hospital deaths were more prevalent than in-hospital deaths: Palmas, São Luís, Rio de Janeiro, Curitiba, Florianópolis, Porto Alegre, and Campo Grande.

Both groups were statistically different for all the studied sociodemographic characteristics (Table 2). When comparing groups, deaths of male patients were more frequent in the out-of-hospital group (57.4% vs 55.5%). Regarding age groups, the out-of-hospital group presented more deaths of individuals aged over 80 years (29.7% vs 26.3%). Married patients had fewer out-of-hospital deaths (38% vs 46%) (Table 2).

Deaths of people with higher levels of schooling (> 12 years) were less prevalent in the in-hospital group than in the out-of-hospital group (11.5% vs 12.8%). Skin color was the characteristic with the smallest difference between groups: a discrete reduction in black individuals was observed in the out-of-hospital group (Table 2).

The negative binomial regression models with fixed effects provided better fit for both groups. AIC values for each model with fixed and random effects are described in Table 3.

For the in-hospital group, the regression model showed that a higher MHDI reduced the incidence of deaths (IRR = 0.44; 95% CI = 0.33–0.58), while higher expected years of schooling were associated with higher incidence (IRR = 1.09; 95% CI = 1.03–1.15).

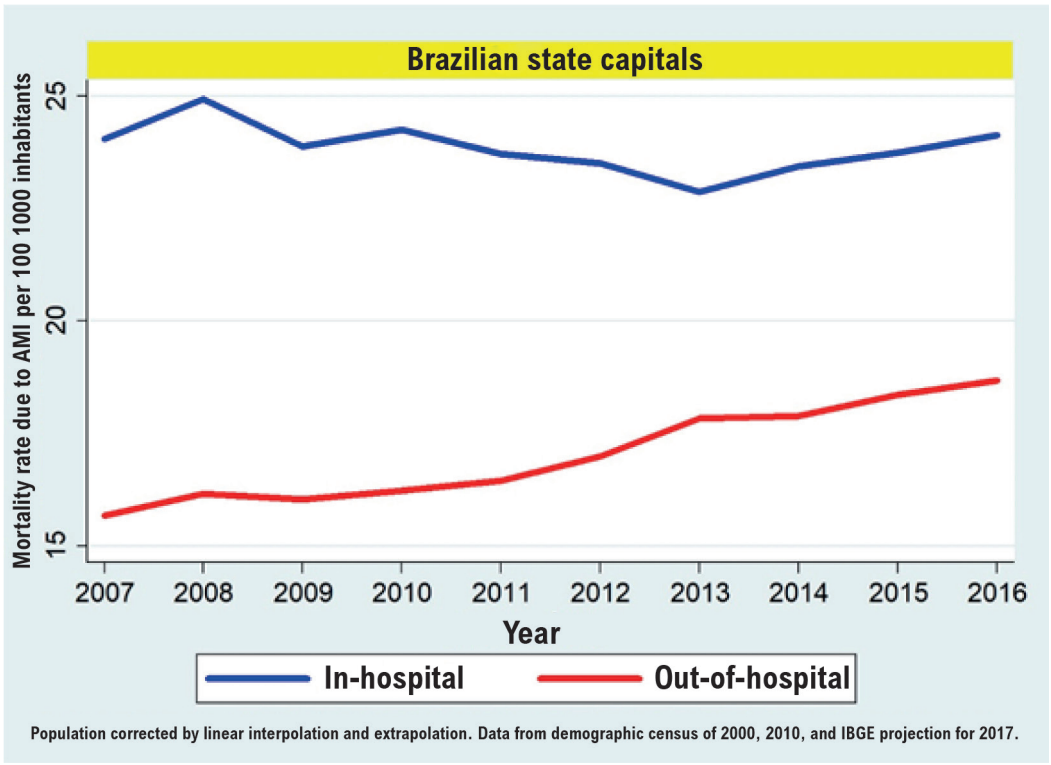


Figure 1 – *Temporal evolution of in- and out-of-hospital mortality rates due to acute myocardial infarction (AMI) per 100 000 inhabitants. Brazilian state capitals, 2007–2016. IBGE: Brazilian Institute of Geography and Statistics. Source: DATASUS. Vital statistics.*

For the out-of-hospital group, residing in the South and Southeast regions increased the incidence of deaths (IRR = 2.84; 95% CI = 1.67–4.85), while higher expected years of schooling were associated with a reduction in deaths (IRR = 0.86; 95% CI = 0.77–0.97).

The Gini coefficient did not present statistically significant differences between groups. The results of regression models for both groups are presented in Table 4.

Discussion

In- and out-of-hospital deaths due to AMI presented differences regarding the sociodemographic characteristics and municipal development indices considered in this study. The assessment of Brazilian state capitals guaranteed that deaths did not happen due to unavailability of specialized care and characterized a nation-wide coverage of the sample, since state capitals account for 23.8% of the Brazilian population.[16]

The prevalence of deaths due to AMI is high. Anatomopathological studies show that, of all out-of-hospital cardiac arrests, AMI is responsible for almost half the deaths when considering all ages; this proportion increases progressively with age.[17] In addition, the association of precordial pain with subsequent cardiac arrest shows near 100% accuracy for AMI diagnosis in some anatomopathological studies.[18] In clinical practice, it is known that aortic dissection, pulmonary thromboembolism, and other acute or potentially acute causes can also progress with precordial pain and death in a short period of time and could be misclassified, but these are much less prevalent than AMI.[3,4]

Few studies have specifically approached out-of-hospital deaths precisely due to the lack of medical records and difficulties in validating data. Most authors consider the SIM as a reliable system[19,20] even though out-of-hospital deaths are more frequently reported as having ill-defined causes, which could represent a lower accuracy of the SIM regarding these events.[21] It is also known that SIM does not provide, as open data, whether the causa mortis was confirmed by the Death Verification Service (SVO), and some state capitals such as Rio de Janeiro, Brasília, and Belo Horizonte had not implemented their own SVO until late 2016.[22]

The literature shows a trend of reduction in mortality rates due to AMI since the 1960s worldwide and since the 1990s in Brazil.[1,3] However, in this study, analysis of the trend curve showed that in-hospital mortality due to AMI is stable, with a slight trend of reduction, while out-of-hospital mortality increased in the studied period. A detailed analysis of these trends can be performed with specific analytic tools, which is not within the scope of this study.

In-hospital mortality rates are higher in the Southeast region, in some capitals of the Northeast region (Natal, João Pessoa, and

Table 1 – Mortality rates due to acute myocardial infarction in Brazilian state capitals from 2007 to 2016 (deaths/100 000 inhabitants). Mean, standard deviation (SD), and minimum (Min) and maximum (Max) recorded values

	In-hospital (H)			Out-of-hospital (OH)			% OH
	Mean	SD	Min – Max	Mean	SD	Min – Max	Mean
Porto Velho	13.12	2.38	10.15 – 18.53	12.14	5.34	6.28 – 22.40	48.06%
Rio Branco	14.17	3.40	10.42 – 19.33	10.04	3.52	5.95 – 14.88	41.47%
Manaus	14.35	1.86	11.71 – 17.32	4.88	2.07	2.22 – 9.10	25.38%
Boa Vista	12.49	2.83	7.39 – 16.18	9.35	1.71	5.63 – 11.61	42.81%
Belém	18.51	3.07	14.99 – 23.47	17.53	3.67	12.49 – 22.39	48.64%
Macapá	10.44	3.26	5.52 – 16.83	4.74	3.56	1.00 – 11.55	31.23%
Palmas	8.68	2.26	4.82 – 11.65	13.43	5.11	5.69 – 22.57	60.74%
São Luís	18.66	2.15	15.96 – 21.93	20.17	4.45	13.30 – 26.90	51.94%
Teresina	21.40	1.85	18.08 – 25.05	13.84	2.96	10.93 – 20.90	39.27%
Fortaleza	16.88	1.33	14.35 – 18.19	6.38	1.86	3.71 – 9.42	27.43%
Natal	23.46	2.68	21.52 – 30.11	23.40	5.75	16.32 – 31.85	49.94%
João Pessoa	25.17	1.70	21.84 – 27.37	21.76	3.01	17.97 – 25.98	46.37%
Recife	43.16	5.54	36.96 – 51.37	21.23	2.21	15.95 – 23.61	32.97%
Maceió	17.77	1.91	14.69 – 20.05	14.20	2.94	10.29 – 18.80	44.42%
Aracajú	17.02	1.82	14.53 – 20.37	11.82	2.80	8.58 – 18.38	40.98%
Salvador	16.19	1.48	13.04 – 17.98	9.47	1.72	6.65 – 13.49	36.91%
Belo Horizonte	15.00	1.48	13.01 – 17.56	9.11	0.60	7.75 – 9.94	37.79%
Vitória	21.70	4.37	15.56 – 27.65	18.34	1.40	16.04 – 19.83	45.80%
Rio de Janeiro	32.68	2.55	29.35 – 38.17	33.75	2.61	27.93 – 36.72	50.81%
São Paulo	36.41	2.07	33.62 – 39.72	17.84	1.73	15.84 – 20.66	32.88%
Curitiba	16.87	1.71	14.56 – 18.84	23.42	1.84	20.49 – 25.86	58.13%
Florianópolis	16.55	2.34	12.58 – 19.84	16.95	4.00	10.92 – 24.22	50.60%
Porto Alegre	23.22	1.65	21.07 – 26.90	30.46	3.18	25.33 – 34.84	56.74%
Campo Grande	18.00	1.70	16.12 – 21.48	33.30	10.59	22.75 – 56.81	64.91%
Cuiabá	20.42	1.78	18.62 – 24.13	15.49	4.72	10.52 – 23.59	43.14%
Goiânia	17.57	2.55	13.44 – 21.89	13.43	3.21	9.52 – 19.34	43.32%
Brasília	15.86	1.19	14.36 – 18.23	7.55	2.46	4.20 – 12.10	32.25%

Source: DATASUS. Vital statistics.

Recife), and in Porto Alegre. On the other hand, out-of-hospital mortality is higher in the South region, in Rio de Janeiro, Campo Grande, and the same northeastern capitals where in-hospital mortality is higher. Recife stood out with a notably high mortality when compared to other northeastern capitals, with a global death rate that was only lower than that of Rio de Janeiro among all capitals.

The main hypothesis of studies explaining higher out-of-hospital mortality is a longer time between symptom onset and arrival at the hospital. A systematic review published in 2010 considered 42 studies and observed that women and older patients took longer to receive hospital treatment.[23] Paradoxically, in our study we observed that out-of-hospital mortality was higher in men and in patients aged over 80 years. More than 70% of deaths occurred among older people (> 60 years), and men presented higher mortality due to AMI in both groups.

Other studies observed that married patients took less time to arrive at the hospital.[24,25] Our results indicated that out-of-hospital mortality was lower in married patients, probably because these had a partner that could help them access hospital care.

Out-of-hospital mortality was slightly higher in patients with higher levels of schooling. Although people with higher levels of schooling have higher survival rates after an AMI,[26,27] this may not significantly affect the acute episode, since initial care by a non-specialist and even self-medication may delay proper care.[28,29]

A higher MHDI is associated with a reduction in in-hospital mortality (IRR = 0.44; 95% CI = 0.33–0.58), with no effect on out-of-hospital mortality. Cities with higher MHDI probably have greater availability and quality of therapeutic resources. Studies that compared countries showed that countries with higher GDP had higher availability of therapeutic resources and lower mortality by AMI.[30] Similarly, spatial analyses performed in

Table 2 – Sociodemographic distribution of in- and out-of-hospital deaths due to acute myocardial infarction. Brazilian state capitals, 2007–2016

	In-hospital			Out-of-hospital			p-value *
	n (110 549)	%	Z†	n (79 085)	%	Z†	
Sex							< 0.001
Male	61304	55.45	-3.58	45389	57.39	4.24	
Female	49245	44.55	4.06	33696	42.61	-4.81	
Age Group							< 0.001
< 1 year	50	0.05	3.43	3	0	-4.06	
1 – 4 years	3	0	0.95	0	0	-1.12	
5 – 9 years	2	0	0.19	1	0	-0.22	
10 – 14 years	14	0.01	-0.15	11	0.01	0.18	
15 – 19 years	207	0.19	3.73	67	0.08	-4.42	
20 – 29 years	685	0.62	0.97	447	0.57	-1.14	
30 – 39 years	1877	1.7	-6.02	1821	2.31	7.12	
40 – 49 years	6991	6.33	-6.10	5904	7.47	7.22	
50 – 59 years	17 580	15.91	-0.98	12 788	16.19	1.16	
60 – 69 years	25 204	22.81	4.73	16 745	21.20	-5.60	
70 – 79 years	28 847	26.10	10.22	17 729	22.45	-12.09	
≥ 80 years	29 052	26.29	-9.02	23 471	29.72	10.67	
Marital status							< 0.001
Single	20 517	19.73	-17.49	19 489	25.82	20.53	
Married	47 417	45.60	15.72	28 719	38.05	-18.46	
Widowed	28 478	27.39	-0.53	20 826	27.59	0.62	
Separated	7575	7.28	-6.10	6448	8.54	7.16	
Schooling							< 0.001
Illiterate	9365	10.77	-1.01	7190	11.02	1.17	
1 – 3 years	25 243	28.92	5.87	17 315	26.55	-6.78	
4 – 7 years	23 509	27.04	-1.71	18 079	27.72	1.98	
8 – 11 years	18 941	21.79	-0.34	14 275	21.89	0.39	
≥ 12 years	9982	11.48	-4.94	8366	12.83	5.71	
Skin color / ethnicity							< 0.001
White	64 689	61.21	0.45	46 734	60.96	-0.53	
Black	7791	7.37	1.79	5383	7.02	-2.10	
Yellow	950	0.9	-1.98	798	1.04	2.33	
Brown	32 186	30.46	-1.17	23 715	30.93	1.37	
Indigenous	60	0.06	0.35	39	0.05	-0.41	

** Chi-squared test. † Standardized residuals of the chi-squared test. Source: DATASUS. Vital statistics.*

Brazilian cities showed an increase in mortality by AMI in poorer neighborhoods.[7,31,32] A spatial analysis performed in Rio de Janeiro observed that lower HDI, calculated for each neighborhood, was an important risk factor for deaths due to cerebrovascular diseases, which share their physiopathology and risk factors with AMI.[8]

Residing in the South and Southeast regions increased the incidence of out-of-hospital deaths (IRR = 2.84; 95% CI = 1.67–4.85). We observed that, in all capitals of the South region and in Rio de Janeiro, out-of-hospital deaths were more prevalent than in-hospital deaths. This finding can be explained by various hypotheses. One of them is that health care services in these regions are better equipped, which could partially explain the reduction in in-hospital deaths in cities with a higher MHDI. Since the in-hospital mortality rate is lower, deaths of patients that could not receive timely care prevailed.

Another hypothesis is that some of these capitals present a larger older population, more susceptible to AMI and with lower locomotion abilities, in addition to the fact that

Table 3 – Akaike Information Criterion (AIC) values for the Poisson and negative binomial regression models* regarding deaths due to acute myocardial infarction occurred in Brazilian state capitals from 2007 to 2016 in the in- and out-of-hospital groups

	In-hospital		Out-of-hospital	
	Poisson	Negative binomial	Poisson	Negative binomial
Fixed effects	2344	2137	3458	2339
Random effects	2778	2565	3893	2777

** Independent variables: residing in the South and Southeast regions, municipal human development index, expected years of schooling, and Gini coefficient.*

Table 4 – Results of negative binomial multiple regression models with temporal adjustment according to the place of occurrence of deaths due to acute myocardial infarction in each of the Brazilian state capitals from 2007 to 2016. Models were weighted by the population of each capital and analyzed with fixed effects.

	In-hospital			Out-of-hospital		
	IRR*	p	CI (95%)	IRR*	p	CI (95%)
South/Southeast regions	0.90	0.752	0.49; 1.67	2.84	< 0.001	1.67; 4.85
MHDI†	0.44	< 0.001	0.33; 0.58	1.26	0.347	0.77; 2.07
Expected years of schooling	1.09	0.004	1.03; 1.15	0.86	0.017	0.77; 0.97
Gini coefficient‡	0.28	0.102	0.60; 1.28	1.02	0.988	0.05; 20.39

** IRR: incidence rate ratio. † MHDI: municipal human development index. ‡ Gini coefficient: assesses inequality in income distribution. Higher values demonstrate higher inequality.*

these cities are larger and more densely populated, which could represent a great logistical challenge regarding the access to health care services and fast transportation of sick patients.[21,33] Moreover, the unhealthy lifestyle, inadequate diet, and higher smoking rate, daily stress, and physical inactivity rate associated with excessive urbanization may increase the risk of AMI,[34-36] which could also justify higher mortality rates due to AMI in these cities.

Expected years of schooling showed opposite results between in- and out-of-hospital groups. Capitals with higher expected years of schooling presented more in-hospital deaths (IRR = 1.09; 95% CI = 1.03–1.15) and less out-of-hospital deaths (IRR = 0.86; 95% CI = 0.77–0.97). The AFIRMAR study considered risk factors for AMI in Brazil and showed that higher schooling was correlated with a lower risk of AMI (odds ratio [OR] = 0.68; p = 0.0239) only when the patient's income was higher.[37] Although in our study there were more out-of-hospital deaths among patients with higher levels of schooling, the inhabitants of a city with higher expected years of schooling probably have better access to information, with better knowledge on signs and symptoms, resulting in a change from out-of-hospital deaths to in-hospital deaths.

Strengths of this study include new contributions to understanding the dynamics of deaths by AMI, especially the out-of-hospital ones, which are little known. The choice of state capitals as sample guarantees the representation of every Brazilian federative unit and coverage of 23.8% of the Brazilian population.

The use of negative binomial regression models with temporal adjustment and weighted by population size has the advantage of letting each capital have its own intercept, serving as its own control, which allows the adjustment for unmeasured variables that do not change with time, in addition to the possibility of directly modelling the number of events instead of rates, which can suffer variations according to changes in numerators and denominators.

Limitations of this study include the use of an ecological and convenience approach for analyzing a time series, in addition to the lower quality of data regarding out-of-hospital deaths. Another limitation involved the use of municipal development indices obtained by the demographic census that, although consist of an alternative for estimation, do not consider the variations and fluctuations that occurred during the interval between data collections.

Conclusion

This study brought new information regarding deaths by AMI in state capitals. In- and out-of-hospital deaths presented differences in temporal trends, sociodemographic characteristics, MHDI, expected years of schooling, and whether patients resided in the South and Southeast regions.

As opposed to what is reported by the literature regarding global mortality by AMI, out-of-hospital mortality is increasing in Brazilian capitals. In comparison with the in-hospital group, out-of-hospital mortality affected more men, people older than 80 years, and unmarried people. Schooling was a factor that converted out-of-hospital mortality into in-hospital mortality. Residing in the South and Southeast regions was associated with a higher incidence of out-of-hospital deaths, while higher MHDI was associated with a lower incidence of in-hospital deaths with no statistically significant effect on out-of-hospital deaths. Further studies are necessary to verity if these differences also happen in other cities, where conditions for AMI treatment are generally more precarious.

Data presented in this study have helped us better understand the reality and trends of mortality in Brazilian state capitals and may contribute to guiding public policies for reducing mortality due to the most prevalent cause of death.

Author Contributions

Conception and design of the research: Abreu SLL, Branco MRFC, Santos AM; Acquisition of data: Abreu SLL; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual contente: Abreu SLL, Abreu JMF, Branco MRFC, Santos AM; Statistical analysis: Abreu SLL, Santos AM; Writing of the manuscript: Abreu SLL, Branco MRFC, Santos AM.

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 Sterffeson Lamare Lucena de Abreu, from Programa de Pós-Graduação em Saúde Coletiva da Universidade Federal do Maranhão.

References

1. World Health Organization. WHO.\ Disease burden and mortality estimates. World Health Organization; 2018. Disponível em: http://www.who.int/healthinfo/global_burden_disease/estimates/en/. Acesso em: 16 set. 2018.
2. Brasil.Ministerio da Saúde. . Minsitério da Sáude. Informações em saúde – Tabnet. Estatísticas vitais. Departamento de Informática do SUS. Disponível em: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sim/cnv/obt10br.def. Acesso em: 16 set. 2018.
3. Reed GW, Rossi JE, Cannon CP. Acute myocardial infarction. Lancet. 2017; 389(10.065): 197-210.
4. Piegas L, Timerman A, Feitosa G et al. V Diretriz da Sociedade Brasileira de Cardiologia sobre tratamento do infarto agudo do miocárdio com supradesnível do segmento ST. Arq Bras Cardiol. 2015; 105(2): 1-105.:1-105.
5. Feres F, Costa R, Siqueira D et al. Diretriz da Sociedade Brasileira de Cardiologia e da Sociedade Brasileira de Hemodinâmica e Cardiologia Intervencionista sobre intervenção coronária percutânea. Arq Bras Cardiol. 2017; 109(1)1-81:.1-81.
6. Godoy MF, Lucena JM, Miquelin AR et al. Mortalidade por doenças cardiovasculares e níveis socioeconômicos na população de São José do Rio Preto, estado de São Paulo, Brasil. Arq Bras Cardiol.2007; 88(2): 200-6.
7. Melo E, Carvalho M, Travassos C. Distribuição espacial da mortalidade por infarto agudo do miocárdio no Município do Rio de Janeiro, Brasil. Cad Saude Publ. 2006; 22(6): 1.225-36.
8. Baena CP, Luhm KR, Costantini CO. Tendência de mortalidade por infarto agudo do Miocárdio em Curitiba (PR) no Período de 1998 a 2009. Arq Bras Cardiol. 2012;98(3) 98(3): 211-7.
9. Dudas K, Lappas G, Stewart S, Rosengren A. Trends in out-of-hospital deaths due to coronary heart disease in Sweden (1991 to 2006). Circulation. 2011; 123(1): 46-52.
10. Fathi M, Rahiminiya A, Zare MA, Tavakoli N. Risk factors of delayed pre-hospital treatment seeking in patients with acute coronary syndrome: A prospective study. Turkiye Acil Tip Derg. 2015; 15(4):163-7.
11. Brasil.Ministério da Saúde. Informações em Saúde – Tabnet. CNES – Estabelecimentos. Classificação do Serviço. 2018. Disponível em: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?cnes/cnv/servc2br.def. Acesso em: 16 set. 2018.
12. Brasil.Ministério da Saúde. Download | Atlas do Desenvolvimento Humano no Brasil. 2013. Disponível em: http://www.atlasbrasil.org.br/2013/pt/download/. Acesso em: 16 set. 2018.
13. Diggle PJ, Heagerty P, Liang KY, Zeger S. Analysis of longitudinal data. Oxford Univesity Press. 2002; 90(431): 1-20.
14. Cameron AC, Trivedi PK. Regression analysis of count data book. Cambridge university press. 2013;53.
15. Brasil. Ministério da Saúde. Resolução nº 466, de 12 de Setembro de 2012. Diário Oficial da Republica Federativa do Brasil. 2012. p. 59. Disponível em: http://bvsms.saude.gov.br/bvs/saudelegis/cns/2013/res0466_12_12_2012.html. Acesso em: 16 set. 2018.
16. Instituto Brasileiro de Geografa e Estatística. Agência de Notícias | IBGE divulga as estimativas populacionais dos municípios para 2017. 2017. Disponível em: https://agenciadenoticias.ibge.gov.br/agencia-sala-de-imprensa/2013-agencia-de-noticias/releases/16131-ibge-divulga-as-estimativas-populacionais-dos-municipios-para-2017. Acesso em: 30 set. 2018.
17. Wu Q, Zhang L, Zheng J et al. Forensic pathological study of 1656 cases of sudden cardiac death in Southern China. Med (United States). 2016; 95(5): 1-8.
18. Stalioraityte E, Bluzas J, Mackiewicz Z et al. Out-of-hospital coronary heart disease death: acute pathological lesions. Acta Cardiol. 2008; 63(4): 423-9.
19. Haraki CA, Gotlieb SL, Laurenti R. Confiabilidade do Sistema de Informações sobre Mortalidade em município do Sul do Estado de São Paulo. Rev Bras Epidemiol. 2005; 8(1): 19-24.
20. Nogueira LT, Rêgo CF, Gomes KR, Campelo V. Confiabilidade e validade das Declarações de Óbito por câncer de boca no Município de Teresina, Piauí, Brasil, no período de 2004 e 2005. Cad Saúde Publ. 2009; 25(2): 366-74.
21. De Abreu DM, Sakurai E, Campos LN. A evolução da mortalidade por causas mal definidas na população idosa em quatro capitais brasileiras, 1996-2007. Rev Bras Estud Popul. 2010; 27(1): 75-88.
22. Conselho Federal de Medicina CFM. Serviços de verificação de óbito: após 10 anos, Brasil não cumpre meta, diz CFM. 2016. Disponível em: https://portal.cfm.org.br/index.php?option=com_content&view=article&id=26393: 2016. Acesso em: 19 set. 2018.
23. Nguyen HL, Saczynski JS, Gore JM, Goldberg RJ. Age and sex differences in duration of prehospital delay in patients with acute myocardial infarction a systematic review. Circ Cardiovasc Qual Outcomes. 2010; 3(1): 82-92.
24. Franco B, Rabelo ER, Goldemeyer S, Souza EN. Patients with acute myocardial infarction and interfering factors when seeking emergency care: implications for health education. Rev Lat Am Enfermagem. 2008; 16(3): 414-8.
25. Bastos AS, Beccaria LM, Contrin LM, Cesarino CB. Time of arrival of patients with acute myocardial infarction to the emergency department. Rev Bras Cir Cardiovasc. 2012; 27(3): 411-8.
26 Consuegra-Sánchez L, Melgarejo-Moreno A, Galcerá-Tomás J et al. Nivel de estudios y mortalidad a largo plazo en pacientes con infarto agudo de miocardio. Rev Esp Cardiol. 2015;68(11): 935-42.

27. Koopman C, Bots ML, Van Oeffelen AA et al. Population trends and inequalities in incidence and short-term outcome of acute myocardial infarction between 1998 and 2007. Int J Cardiol. 2013; 168(2): 993-8.

28. Farshidi H, Rahimi S, Abdi A et al. Factors associated with pre-hospital delay in patients with acute myocardial infarction. Iran Red Crescent Med J. 2013; 15(4): 312-6.

29. Nilsson G, Mooe T, Söderström L, Samuelsson E. Pre-hospital delay in patients with first time myocardial infarction: an observational study in a northern swedish population. BMC Cardiovasc Disord. 2016; 16(1): 1-10.

30. Orlandini A, Díaz R, Wojdyla D et al. Outcomes of patients in clinical trials with ST-segment elevation myocardial infarction among countries with different gross national incomes. Eur Heart J. 2006; 27(5): 527-33.

31. Caetano E, Melo P. Infarto agudo do miocárdio no município do Rio de Janeiro: qualidade dos dados, sobrevida e distribuição espacial por infarto agudo do miocárdio no município do Rio de Janeiro: qualidade. 2004; 16: 121-3.

32. Luiz SB, Achutti A, Inês AM, Azambuja MI, Bassanesi SL. Mortalidade precoce por doenças cardiovasculares e desigualdades sociais em Porto Alegre: da evidência à ação. Arq Bras Cardiol. 2007; 90(6): 403-12.

33. Beig JR, Tramboo NA, Kumar K et al. Components and determinants of therapeutic delay in patients with acute ST-elevation myocardial infarction: a tertiary care hospital-based study. J Saudi Hear Assoc. 2017; 29(1): 7-14.

34. Ribeiro AG. The promotion of health and integrated prevention of risk factors for cardiovascular diseases. Cien Saude Colet. 2012; 17(1): 7-17.

35. Buss PM. Globalização, pobreza e saúde. Cien Saude Colet. 2007; 12(6): 1.575-89.

36. Gama LC, Biasi LC, Ruas A. Prevalência dos fatores de risco para as doenças cardiovasculares em pacientes da rede SUS da UBS Progresso da cidade de Erechim. Perspect Erechim. 2012; 36(133): 63-72.

37. Piegas LS, Avezum A, Pereira JC et al. Risk factors for myocardial infarction in Brazil. Am Heart J. 2003; 146(2): 331-8.

Acute Myocardial Infarction Death Rates in Brazil - A Small Light at the End of the Tunnel

Ana Teresa Timóteo[1,2]

Hospital Santa Marta, Centro Hospitalar Universitário Lisboa Central,[1] *Lisboa - Portugal*
NOVA Medical School - Faculdade de Ciências Médicas,[2] *Lisboa – Portugal*

Short Editorial related to the article: In- and Out-of-Hospital Deaths by Acute Myocardial Infarction in Brazilian State Capitals

Epidemiological studies are the mainstay to better understand and plan regional healthcare. It is also very important to implement programs for quality-of-care evaluation and improvement. To fulfill that last objective, prospective registries and retrospective analysis of real-life clinical practices are essential. Continuous national registries can support continuous quality improvement at the hospital and country level and have proven to be effective in both Europe and North America.[1] These systems use continuous data collection and provide online reports focusing on the processes of care and outcomes concerning common cardiovascular diseases and interventions.[1] Another approach is to use data from non-dedicated national healthcare databases. However, most databases were not developed for such specific analysis and information is rather limited.

Lucena de Abreu et al.[2] present an interesting study in this journal.[2] They analyzed in-hospital and out-of-hospital death rates by acute myocardial infarction (AMI) from 2007 to 2016 in 27 Brazilian state capitals, representing approximately 24% of the Brazilian population. This topic is important, given that, in a literature review of medical journals over the past ten years, this information is lacking, and, for this reason, the reality in South America is virtually unknown. The last information available was a study published in 2020 with a retrospective review of temporal trends on mortality due to acute myocardial infarction in Brazil from 1996 to 2016, which showed a general decrease, especially in the capital cities, but regional inequalities were also observed.[3]

In the present study,[2] the authors analyzed data from the Mortality Information System of DATASUS. In a temporal analysis, they found that in-hospital deaths due to AMI, reported as a mortality rate per 100.000 inhabitants, had a very low decrease over time. By contrast, out-of-hospital deaths due to AMI steadily increased, but it is still lower, when compared to in-hospital deaths. Despite this, globally, 42% of AMI deaths were out-of-hospital. Data showed a very large variability between state capitals, and some differences were also found regarding socioeconomic variables between in-hospital and out-of-hospital deaths. Particularly, out-of-hospital deaths were more incident in males, octogenarians, and single individuals. In-hospital death was inversely associated with a higher Municipal Human Development Index, which was an expected finding, because a higher index can be related to better hospitals and quality of care. Surprisingly, they also found a direct association with expected years of schooling, with individuals with longer years of school showing higher death rates. We would expect that those individuals with higher economic income would resort more easily to better equipped hospitals, but this result is probably biased. No multivariate adjustment was made, and a possible negative impact might have resulted from data from major capital cities, like São Paulo or Rio de Janeiro, with the highest death rates, associated with a very large population, important economic disparities, and differences in health care access, but also higher school years compared to other capitals. Out-of-hospital deaths were inversely associated with expected years of schooling, as we might expect from difficulties in healthcare access, and directly associated with South and Southeast regions. This regional difference mandates a full characterization of regions to understand the main differences found between them, and this is not clarified in the present manuscript.[2]

Of particularly relevance, is the finding that both in-hospital and out-of-hospital death rates per 100.000 inhabitants are extremely high in the main capitals, Rio de Janeiro, and São Paulo. Although quality of care is expected to be better in those two capitals, the high population rate, with a significant proportion from a very low socioeconomic background, can be associated with major difficulties and delays in healthcare access. Another important finding is that out-of-hospital death rates by AMI are higher in the South and Southeast capitals, as well as in Rio de Janeiro.

This study[2] shed some light on the understanding of the dynamics of death rates by AMI, particularly regarding those occurring out-of-hospital, because this has not been previously addressed. However, important limitations are present. As the authors mentioned, the specific cause of death in out-of-hospital deaths, excluding death by trauma or infectious diseases, is usually not very precise. It lacks clinical data, because most cases are not submitted to autopsy and death certificates are in fact the result of an educated guess. In older age groups, AMI or stroke are probably the most frequent diagnosis in death certificates without clinical confirmation. It is true that most out-of-hospital cardiac arrests are caused by AMI, particularly when it is possible to retrieve an information of previous precordial pain. But there are other causes for precordial pain that are as deadly or even more deadly, when compared with AMI. If aortic dissection is

Keywords

Myocardial Infarction; Mortality; Hospitalization; Epidemiology; Brazil; Time Series Studies.

Mailing Address: Ana Teresa Timóteo •
Hospital Santa Marta - Rua Santa Marta, 1110, Lisboa – Portugal
E-mail: ana_timoteo@yahoo.com

DOI: https://doi.org/10.36660/abc.20210446

rather rare, acute pulmonary embolism is somewhat a frequent and very often overlooked cause of precordial pain and cardiac arrest. This study also showed the reality of urban areas, but it lacks national representativeness, because more that 75% of the Brazilian population was not included.

For all these reasons, this first study opens a window on that subject, but additional studies are essential for a complete characterization. It is important to address inequalities between capitals, particularly in healthcare access, and it is also very important to fully characterize the exact cause of death in out-of-hospital deaths. It is essential to uncover how biased death certificates are. Death rate information should be complemented with data from national registries, the only possible way to obtain complete and accurate information. With this, it will be possible to implement a quality improvement program in the country to address inequalities and to optimize the identified problems.

References

1. Wallentin L, Gale CP, Maggioni A, Bardinet I, Casadei. EuroHeart: European Unified Registries On Heart Care Evaluation and Randomized Trials: An ESC project to develop a new IT registry system which will encompass multiple features of cardiovascular medicine. Eur Heart J .2019;40(33):2745-9.
2. Abreu SLL, Abreu JMF, Branco MRFC, Santos AM. In- and Out-of-Hospital Deaths by Acute Myocardial Infarction in Brazilian State Capitals. Arq Bras Cardiol. 2021; 117(2):319-326. doi: https://doi.org/10.36660/abc.20200043
3. Martins Ferreira LC, Nogueira MC, Carvalho MS, Bustamante Teixeira MT. Mortalidade por infarto agudo do miocárdio no Brasil de 1996 a 2016: 21 anos de contrastes nas regiões brasileiras. Arq Bras Cardiol. 2020; 115(5):849-59.

Cardiovascular and Cancer Death Rates in the Brazilian Population Aged 35 to 74 Years, 1996-2017

Antonio de Padua Mansur[1] *and Desiderio Favarato*[1]

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

Abstract

Background: Cardiovascular diseases (CVD) and cancer are the main causes of death worldwide. These diseases share many risk factors. Control of traditional risk factors for CVD was associated with lower incidence of cancers.

Objective: To analyze CVD and cancer mortality rate trends in Brazilian population aged 35-74 years from 1996 to 2017.

Methods: Crude and age-adjusted death rate trends were analyzed for all causes of death, CVD, and cancer. Data were obtained from mortality database of the Ministry of Health. Joinpoint Regression Program performed analysis of trends and adjustments in death rates. The degree of changes was determined by the average annual percent change (AAPC). Level of statistical significance was set at p <0.05.

Results: Mortality from all causes of death (AAPC=-1.6%; p<0.001), CVD (AAPC=-2.3; p<0.001), ischemic heart disease (IHD) (AAPC=-1.6; p<0.001) and stroke (AAPC=-3.7; p<0.001) declined. Same trends were observed for CVD (p<0.001) in men and women. Death rates from all causes of cancer (AAPC=-0.1; p=0.201), in men (AAPC=-0.1; p=0.193) and in women (AAPC=-0.1; p=0,871) remained unchanged. In 2002, mortality from cancer exceeded the sum of deaths from IHD and stroke. If trends continue, cancer mortality will also exceed mortality from CVD by 2024. In women, death rates from breast, lung and colon cancer increased, and from cervical and gastric cancers decreased. In men, mortality from lung, stomach and esophagus cancer decreased, and from prostate cancer remained unchanged.

Conclusion: CVD are currently the leading cause of death in Brazil, but death rates from cancer will exceed those from CVD in a few years.

Keywords: Cardiovascular Diseases/mortality; Epidemiology; Mortality; Brazil; Stroke; Neoplasms; Myocardial Ischemia.

Introduction

Cardiovascular diseases (CVD) and neoplasms are the leading causes of death in Brazil and worldwide.[1,2] In 2017, chronic non-communicable diseases (NCD) were responsible for 73.4% of world mortality.[2] It is believed that more than 85% of premature deaths due to NCD, of people aged 30 to 69 years, occurred in low-income countries.[3] Ischemic heart disease (IHD) and stroke accounted for approximately 60% of deaths from CVD. A previous study in Brazil showed a downward trend in mortality from CVD from 1980 to 2012.[4] During this period, stroke mortality reduced more significantly than IHD mortality. Death rate from CVD had important regional variations in Brazil, with the highest rates in the southeast and south regions,[5] and convergence of mortality from IHD and stroke in the five regions. The convergence of death rates in these regions occurred earlier for stroke, around 1999, and later for IHD in 2007.

According to the World Health Organization (WHO), cancers were the second leading cause of death from NCD in the world population.[3] In many developed countries, cancers were the leading cause of death in adults under 70 years of age. In the USA, cancer death rate was higher than CVD death rate in the 45 to 64 age group from 1999 to 2017,[6] and decreased by 27% from 1991 to 2016. From 2007 to 2016, the annual reduction was 1.4% in women and 1.8% in men.[7] In Brazil, cancers were the second leading cause of death in 2017.[1]

CVD and cancers share some risk factors. The main risk factors for CVD are also associated with higher incidence of cancers. Recent meta-analysis showed that each risk factor for CVD – smoking, hypertension, diabetes, obesity, excessive alcohol consumption, physical inactivity and low socioeconomic status – was associated with higher incidence of cancers.[8] On the other hand, control of the main risk factors for CVD was associated with a significant reduction in the incidence of cancer.[9] Therefore, control of CVD risk factors has also a significant impact in reducing cancer death rate.

Mailing Address: Antonio de Padua Mansur•
Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo - Av. Dr. Enéas C. Aguiar, 44.
Postal Code 05403-000, São Paulo, SP – Brazil
E-mail: apmansur@yahoo.com
Manuscript received March 24, 2020, revised manuscript June 29, 2020, accepted August 12, 2020

DOI: https://doi.org/10.36660/abc.20200233

This study analyzed trends in death rates from all causes, CVD, IHD, stroke and cancer in women and men of the Brazilian population from 1996 to 2017.

Methods

We analyzed death rate trends from all causes of diseases, CVD, IHD, stroke and cancers in Brazilian men and women from 1996 to 2017. Crude death rate per 100 000 population was analyzed for each five-year age group between 35 to 74 years. We calculated age-adjusted death rate for this age group per 100 000 population for the study period (1996-2017) using the direct method based on WHO world standard population (2000). Mortality data were obtained from the Vital Health Statistics of the Ministry of Health DATASUS, available online at www2.datasus.gov.br.[10] The causes of death were classified by the 10th revision of the International Classification of Diseases (ICD). CVD were grouped in codes I00 to I99, IHD in codes I20 to I25, stroke in codes I60 to I69 and cancers in codes C00 to C97. The following codes were used for lung, gastric, prostate, esophageal, colon, breast, and cervical cancers, respectively: C34, C15, C61, C15, C18, C50 and C53. The five main causes of death from cancer were analyzed by sex in period from 1996 to 2017.

Statistical Analysis

We used the statistical program *Joinpoint Regression Program* version 4.7.0.0. from the National Cancer Institute, Division of Cancer Control and Population Sciences for analysis of age-adjusted death rate trends.[11] The joinpoint analysis was used to identify the year (independent variable) when significant changes in the mortality rate (dependent variable) occurred during the study period. The degree of the changes was determined by the average annual percent change in death rate (AAPC). Slopes of regression lines of CVD versus cancer and IHD versus stroke were compared using the Microsoft Excel 2010 with t-statistic and two tailed t-distribution.[12] The statistical significance was set at $p < 0.05$. The study did not require ethical approval as mortality data were obtained from a public website and identity of individuals was not known.

Results

CVD and cancer age-adjusted death rate per 100 000 population corresponded to 50% of the death rate from all causes. CVD and cancer accounted for approximately 30% and 20% of total mortality, respectively (Table 1). CVD mortality decreased by 38% from 1996 to 2017 and cancer mortality remained unchanged ($p<0.001$ for comparisons of the slopes of regression lines of CVD versus cancer age-adjusted death rate). In 1996, cancer mortality was 52% lower than CVD mortality but 22% lower in 2017. If these trends continue, cancer mortality will equal CVD mortality in the beginning of 2024 (Figure 1) Likewise, the crude death rate analyzed, every 5 years, for the 35 and 74 age group showed that the mortality from CVD was always higher than cancer death rate (Table 2).

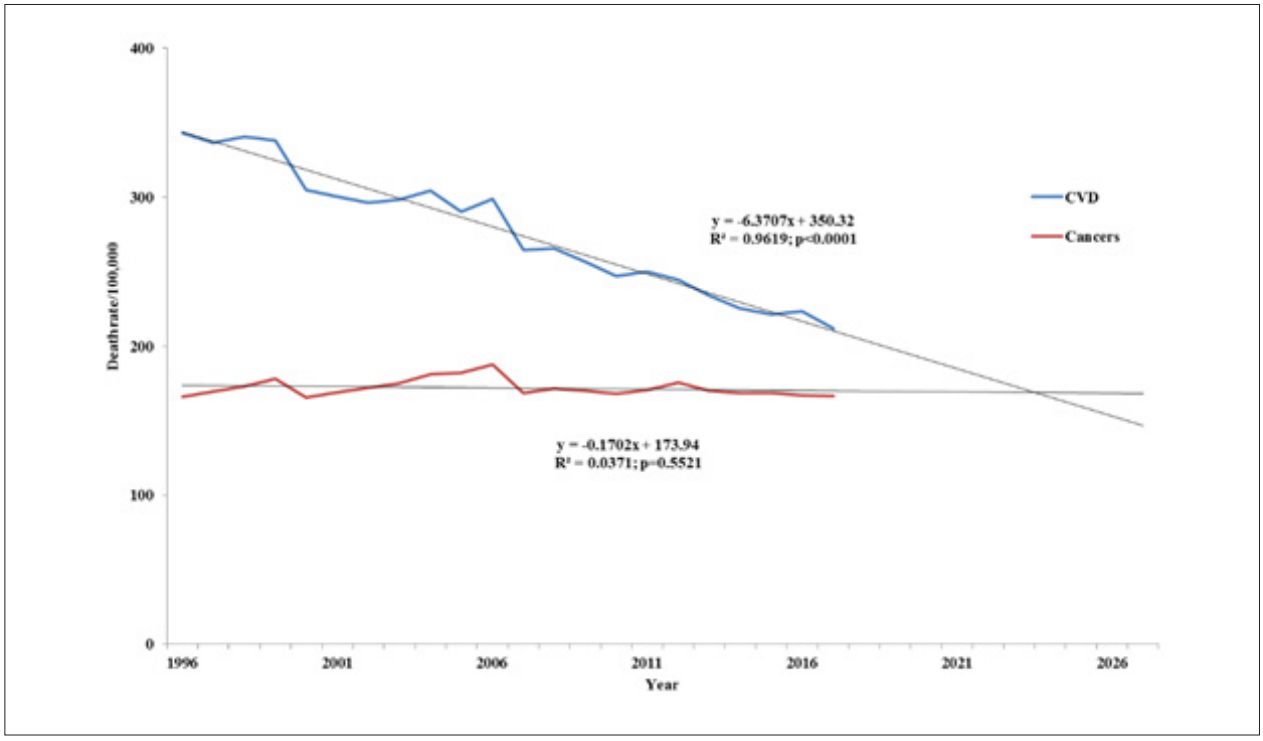


Figure 1 – *Trends in mortality rates from cardiovascular disease (DCV) and cancers in Brazilian population aged 35 to 74 years from 1996 to 2017.*

All-cause mortality

The frequency of the six main causes of death in the Brazilian population is shown in Figure 2. The percentage of CVD decreased, and neoplasms increased in the general population, in both men and women, from 1996 to 2017. In 1996 and 2017, CVD and neoplasms accounted for, respectively, 48.4% and 51.0% of deaths in the general population, 45.0% and 47.4% in men and 53.8% and 56.7% in women. The all-cause mortality rate, adjusted for age (35 to 74 years of age), is described in Table 1. We observed a 28% reduction in age-adjusted all-cause mortality rate in the general population (AAPC = -1.6%; p <0.001) and in both sexes (p<0.001).

The analysis of the crude death rate every five years from 35 to 74 years of age showed a significant reduction in all-cause mortality in all age groups in the general population (p <0.001) and in both sexes (Table 3).

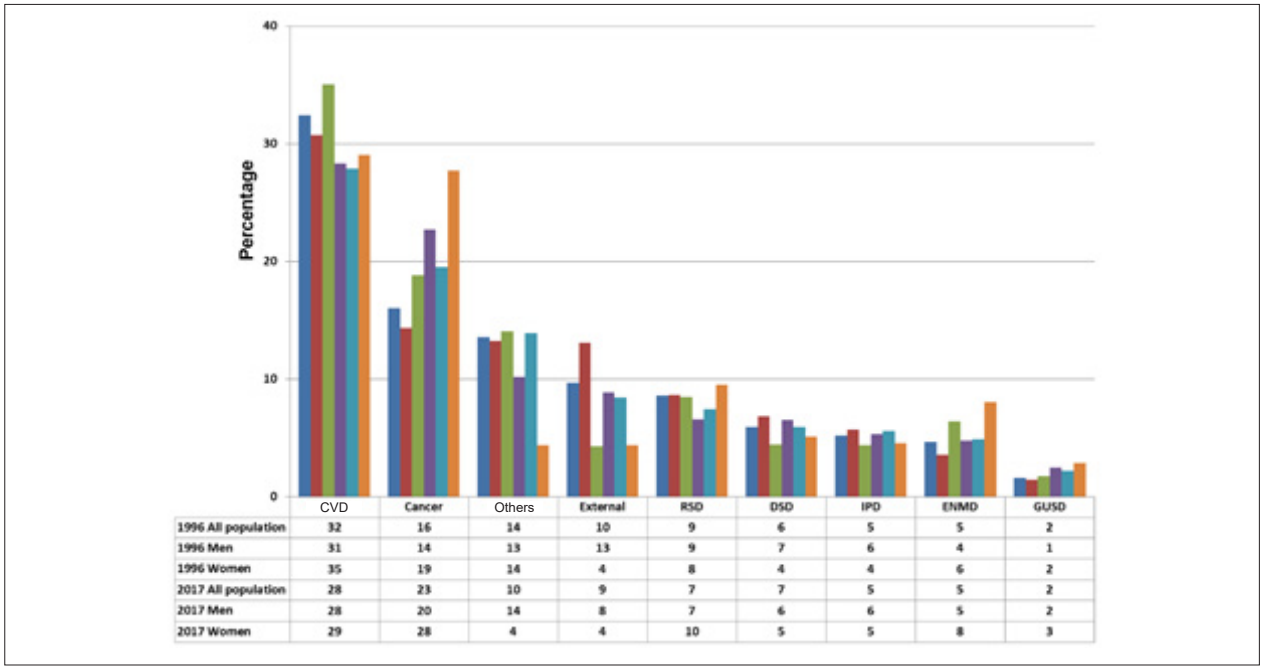
Cardiovascular diseases

The frequencies of the main causes of death from CVD in the general population are displayed in Figure 3. From 1996 to 2017, the percentage of deaths from IHD increased and from stroke decreased in both men and women. For the years 1996 and 2017, IHD and stroke accounted for, respectively, 55.3% and 51.3% of deaths from CVD in the general population, 59.5% and 58.2% in men and to 51.4% and 46.2% in women. The mortality rate from CVD, adjusted for age (35 to 74 years of age) is shown in Table 1. The age-adjusted death rate from CVD corresponded, on average, to 31% of all causes of death, decreasing from 33% in 1996 to 28% in 2017. The main causes of death from CVD were IHD (average of 35% of deaths from CVD), increasing from 33% in 1996 to 37% in 2017, followed by stroke (average of 22% of deaths from CVD), increasing from 18% in 1997 to 25% in 2017. IHD and stroke corresponded on average to 57% of all CVD in the period from 1996 to 2017 (Table 1; Figure 4). Comparisons of the age-adjusted regression slopes of IHD versus stroke showed higher reduction in stroke death rate (-1.58 vs. -2,25, respectively; p<0.001). We observed a significant reduction in age-adjusted death rate for CVD, IHD and stroke in the general population, in both women and men (p <0.0001) (Table 1; Figures 5 and 6). The age-adjusted death rate for IHD and stroke were two times and 1.5 times higher in men, respectively, compared to women. However, comparisons of linear regressions between men and women showed a greater reduction in death rate from CVD, IHD and stroke in men (p <0.0001 for all comparisons).

The analysis of the crude death rate every five years from 35 to 74 years of age showed a significant reduction in all age groups for deaths from CVD, IHD and stroke in the general population (p <0.001) and in both sexes. The reduction was greater for stroke compared with IHD (Tables 2 and 4) There was a significant reduction in the crude death rate from CVD, IHD and stroke for all age groups.

Cancers

The age-adjusted mortality rate from cancer remained unchanged from 1996 to 2017, and corresponded, on average, to 20% of total mortality, increasing from 16% in



	CVD	Cancer	Others	External	RSD	DSD	IPD	ENMD	GUSD
1996 All population	32	16	14	10	9	6	5	5	2
1996 Men	31	14	13	13	9	7	6	4	1
1996 Women	35	19	14	4	8	4	4	6	2
2017 All population	28	23	10	9	7	7	5	5	2
2017 Men	28	20	14	8	7	6	6	5	2
2017 Women	29	28	4	4	10	5	5	8	3

Figure 2 – *Frequencies of the six main causes of death in the Brazilian population. CVD: Cardiovascular disease; DSD: Diseases of the digestive system; ENMD: Endocrine, nutritional and metabolic diseases; External: External causes of morbidity and mortality; GUSD: Diseases of the genitourinary system; IPD: Certain infectious and parasitic diseases; RSD: Diseases of the respiratory system; Others: Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified.*

Table 1 – Age-adjusted mortality rates (per 100 000 population) from cardiovascular diseases, ischemic heart disease, stroke, and cancer in total population, men and women, in Brazil from 1996 to 2017

General population	1996	2017	% change	AAPC(%)	99%CI		p
All causes of deaths	1032.24	744.67	-28	-1.6	-1.8	-1.4	<0.000
Cardiovascular disease	342.85	211.94	-38	-2.3	-2.5	-2.1	<0.001
Ischemic Heart disease	111.46	79.19	-29	-1.6	-1.8	-1.5	<0.001
Stroke	85.5	38.6	-55	-3.7	-3.9	-3.5	<0.001
Ischemic heart disease + stroke	196.96	117.78	-40	-2.4	-2.6	-2.2	<0.001
Cancer	166.13	166.37	0	-0.1	-0.4	0.1	0.2
Men							
All causes of death	1327.36	964.96	-27	-1.6	-1.8	-1.3	<0.000
Cardiovascular disease	421.96	272.35	-35	-2.1	-2.3	-1.9	<0.001
Ischemic Heart disease	150.23	110.52	-26	-1.5	-1.7	-1.3	<0.001
Stroke	102.9	49.13	-52	-3.5	-3.7	-3.3	<0.001
Ischemic heart disease + stroke	253.13	159.65	-37	-2.2	-2.4	-2	<0.001
Cancer	194.36	187.29	-3.7	-0.3	-0.5	-0.1	<0.001
Women							
All causes of death	764.76	548.76	-28	-1.7	-1.9	-1.5	<0.000
Cardiovascular disease	270.84	159.26	-41	-2.5	-2.8	-2.3	<0.001
Ischemic Heart disease	76.25	51.63	-32	-1.9	-2.1	-1.7	<0.001
Stroke	69.81	29.66	-57	-3.9	-4.2	-3.7	<0.001
Ischemic heart disease + stroke	146.07	81.29	-44	-2.8	-3	-2.5	<0.001
Cancer	141.23	149.38	5.8	0.1	-0.1	0.3	0.4

%change: 2017 death rate minus 1996 death rate; AAPC: average annual percentage change; CI: confidence interval.

1996 to 22% in 2017. Mortality from all cancers exceeded mortality from IHD and stroke in the year 2002 (Table 1; Figure 4).

In men, there was a significant reduction in age-adjusted death rate from all cancers in the period ($p<0.001$) and corresponded, on average, to 17% of all-cause mortality, ranging from 15% in 1996 to 19% in 2017. Mortality rate from all cancers in men exceeded the death rate from IHD and stroke in 2008 (Table 1; Figure 5).

Age-adjusted death rate from cancer among women remained unchanged from 1996 to 2017 and corresponded, on average, to 23% of all deaths, increasing from 18% in 1996 to 27% in 2017. The age-adjusted mortality rate from cancer exceeded the death rate from IHD and stroke in the year of 1997 (Table 1; Figure 6). The comparison of the difference of the linear regression lines between men [$y = 203.12 - 0.50$ ($R2 = 0.21$; $p = 0.099$)] and women [$y = 146.82 + 0.16$ ($R2 = 0.05$; $p = 0.276$)] for all cancers was statistically significant ($p = 0.011$) showing declining trend for men and an increasing trend for women.

The main causes of deaths from cancer in men were lung, gastric, prostate, esophagus and colon cancer. From 1996 to 2017, we observed a reduction in age-adjusted death rate for lung, gastric and esophageal cancers, and an increase in colon cancer ($p<0.001$). Death rate from prostate cancer remained unchanged in the period (Table 5; Figure 7).

The main causes of cancer in women were breast, lung, cervical, gastric and colon cancers. From 1996 to 2017, there was reduction in the age-adjusted death rate for cervical and gastric cancers and an increase in breast, lung, and colon cancers ($p<0.001$) (Table 5; Figure 8).

The analysis of death rate from all cancers in five-year periods showed a reduction in mortality for the age group between 35 and 54 years, and no change between 55 and 74 years of age in total population and in men. In women, mortality rate from all cancers reduced only for age groups between 40 and 49 years and between 60 and 69 years. For other age groups, mortality remained unchanged (Table 2).

Discussion

This study showed persistent and gradual reduction in mortality from CVD, IHD and stroke in men and in women. The reduction was more pronounced in men than in women.

Cardiovascular diseases

The decline in CVD mortality in Brazil was similar to that observed in developed countries and in many developing countries. The reduction in mortality was more significant in countries with a higher sociodemographic index.[13] Despite the significant reduction in CVD mortality in the period from 1996

Table 2 – Crude mortality rates (per 100 000 population) from cardiovascular diseases (CVD) and cancer in the general population in Brazil from 1996 to 2017

	Cardiovascular disease						Cancer					
Age group	1996	2017	% change	AAPC(%)	99%CI		1996	2017	% change	AAPC(%)	99%CI	
35 – 39	47,62	26,36	-45	-2.5*	-2.8	-2.2	26,64	25,65	-4	-0.3*	-0.5	-0.1
40 – 44	88,85	49,41	-44	-2.8*	-3.0	-2.7	49,73	43,99	-12	-0.9*	-1.0	-0.7
45 – 49	153,2	87,01	-43	-2.8*	-3.1	-2.6	86,77	76,26	-12	-0.9*	-1.2	-0.6
50 – 54	245,94	146,86	-40	-2.7*	-3.0	-2.4	135,69	130,53	-4	-0.5*	-0.8	-0.2
55 – 59	394,94	229,14	-42	-2.5*	-2.9	-2.2	212,25	209,39	-1	-0.1	-0.4	0.2
60 – 64	614,22	383,33	-38	-2.2*	-2.4	-2.0	306,56	316,44	3	0.1	-0.1	0.2
65 – 69	936,57	599,92	-36	-2.1*	-2.3	-1.9	431,34	441,09	2	0.1	-0.1	0.3
70 – 74	1449,9	952,99	-34	-2.0*	-2.2	-1.8	566,21	610,74	8	0.2	-0.0	0.4
Men												
35 – 39	57,21	32,28	-44	-2.4*	-2.8	-2.1	21,47	18,25	-15	-1.0*	-1.2	-0.8
40 – 44	109,8	60,55	-45	-2.8*	-3.1	-2.6	44,29	34,95	-21	-1.5*	-1.7	-1.2
45 – 49	188,97	106,62	-44	-2.8*	-3.1	-2.6	87,5	68,5	-22	-1.5*	-1.9	-1.1
50 – 54	188,97	106,62	-44	-2.8*	-3.1	-2.6	146,38	130,76	-11	-0.8*	-1.1	-0.4
55 – 59	501,07	302,72	-40	-2.4*	-2.7	-2.1	248,35	226,81	-9	-0.3	-0.7	0.0
60 – 64	775,24	501,75	-35	-2.0*	-2.3	-1.8	377,57	374,18	-1	-0.1	-0.3	0.1
65 – 69	1151	777,83	-32	-1.9*	-2.0	-1.7	541,39	541,7	0	-0.1	-0.3	0.1
70 – 74	1715,4	1207,8	-30	-1.7*	-1.9	-1.4	725,44	779,78	7	0.2	-0.0	0.5
Women												
35 – 39	38,45	20,5	-47	-2.6*	-3.0	-2.3	31,52	32,98	5	0.2	-0.1	0.5
40 – 44	68,57	38,54	-44	-2.9*	-3.1	-2.7	54,91	52,82	-4	-0.4*	-0.6	-0.3
45 – 49	118,44	68,14	-42	-2.8*	-3.1	-2.6	86,06	83,7	-3	-0.4*	-0.7	-0.0
50 – 54	118,44	68,14	-42	-2.8*	-3.1	-2.6	125,55	130,31	4	-0.2	-0.6	0.1
55 – 59	296,71	161,73	-45	-2.7*	-3.1	-2.4	179,35	193,43	8	0.2	-0.1	0.5
60 – 64	468,94	278,6	-41	-2.5*	-2.7	-2.3	243,39	265,39	9	0.3*	0.1	0.5
65 – 69	748,39	449,47	-40	-2.4*	-2.6	-2.1	336,33	356,04	6	0.3*	0.1	0.5
70 – 74	1218,50	751,48	-38	-2.4*	-2.6	-2.1	430,65	477,05	11	0.2	-0.1	0.4

*%change: 2017 death rate minus 1996 death rate; AAPC: average annual percentage change; CI: confidence interval; *p<0.001*

to 2017, the death rate from CVD in age groups between 35 and 74 years in Brazil remained higher when compared to other countries. In Brazil, in 2017, the mortality rate in men was close to that the death rate seen in US men in the latest update of the American Heart Association (AHA).[14] Countries with the highest CVD death rates in men were, in decreasing order, Belarus, Ukraine, Russia, Romania, Hungary, Serbia, Slovakia, Croatia and Czech Republic. CVD death rate in women in Brazil in 2017 was even worse when compared to death rate in men, ranking behind only the Ukraine, Russia, Belarus, Serbia and Romania according to the latest AHA statistical update.[14] Previous study in Brazilian population showed stabilization in the trend in mortality from IHD from 2007 to 2012.[4] This same trend stabilization in IHD death rates was observed in other countries and it was associated with increased incidence of obesity and diabetes in the population.[15,16] It is estimated that one of two individuals will be obese by 2030 in USA.[17] It is believed that the increase in the incidence of these risk factors was responsible for the slowdown in the downward trend in mortality from CVD in the USA in the period from 2010 to 2017.[18] Our data, however, indicated that in Brazil, starting from 2013, there was a resumption of the downward trend of CVD death rate, probably resulting from a lower prevalence of smoking and better hypertension control.

Cancer

Trends in mortality rates from all cancers remained unchanged from 1996 to 2017. The main causes of cancer death in women were breast, lung, cervical and stomach from 1996 to 2012 and colon from 2013 to 2017. Increasing trends in mortality rates from breast, lung and colon cancers and decreasing trends in deaths from stomach cancer were observed. The main causes of deaths from cancer in men were lung, stomach, prostate and esophageal cancer, with

Table 3 – Crude mortality rates per 100 000 population from all causes of death in the general population in Brazil from 1996 to 2017

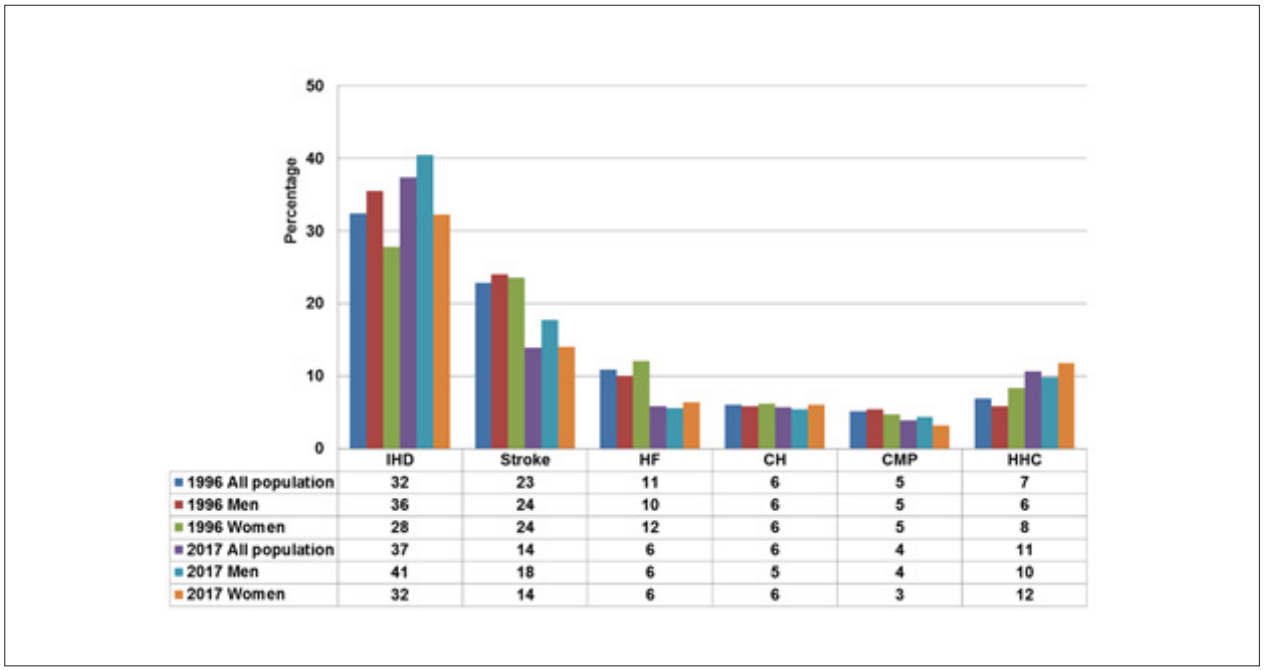
General population	1996	2017	% change	AAPC(%)	99%CI	
35 – 39	462,36	289,21	-37	-1.8*	-2.0	-1.6
40 – 44	577,73	363,58	-37	-2.0*	-2.2	-1.9
45 – 49	757,12	499,16	-34	-2.0*	-2.2	-1.7
50 – 54	1029,54	730,39	-29	-1.8*	-2.1	-1.6
55 – 59	1487,2	1062,17	-29	-1.7*	-1.9	-1.4
60 – 64	2137,66	1614,4	-24	-1.5*	-1.7	-1.3
65 – 69	3118,78	2374,82	-24	-1.5*	-1.7	-1.3
70 – 74	4550,93	3605,81	-21	-1.4*	-1.7	-1.1
Men						
35 – 39	462,36	289,21	-37	-2.0*	-2.2	-1.8
40 – 44	577,73	363,58	-37	-2.2*	-2.3	-2.0
45 – 49	757,12	499,16	-34	-2.0*	-2.3	-1.7
50 – 54	1029,54	730,39	-29	-1.8*	-2.1	-1.5
55 – 59	1487,2	1062,17	-29	-1.6*	-2.0	-1.3
60 – 64	2137,66	1614,4	-24	-1.4*	-1.7	-1.1
65 – 69	3118,78	2374,82	-24	-1.4*	-1.6	-1.1
70 – 74	4550,93	3605,81	-21	-1.2*	-1.5	-0.9
Women						
35 – 39	180,12	125,12	-30	-1.5*	-1.8	-1.2
40 – 44	260,07	178,54	-31	-1.8*	-2.0	-1.6
45 – 49	388,86	267,28	-31	-1.9*	-2.1	-1.6
50 – 54	568,95	400,78	-30	-1.9*	-2.2	-1.6
55 – 59	855,6	599,49	-30	-1.7*	-2.0	-1.4
60 – 64	1273,52	928,53	-27	-1.6*	-1.8	-1.4
65 – 69	1951,63	1408,09	-28	-1.6*	-1.8	-1.4
70 – 74	3031,34	2257,57	-25	-1.6*	-1.8	-1.3

*%change: 2017 death rate minus 1996 death rate; AAPC: average annual percentage change; CI: confidence interval; *p<0.001*

decreasing trends in lung and stomach cancer death rates, but unchanged trends in mortality from prostate and esophageal cancers. The main causes of death from cancers, but not the trends in death rates, are close to those observed in developed countries, where lung cancer was the most important cause of death followed by prostate cancer in men and breast cancer in women.[19-22] Since 1990 and contrary to what was observed in Brazil, decreasing trends in mortality rates from main cancers were observed in men (lung, prostate and colon cancer) and in women (lung, breast and colon cancer) in the United States. The most recent analysis of the death rate from cancer in USA showed a significant reduction of 2.2% between 2016 and 2017, and attributed, in large part, to the reduction in lung cancer mortality.[23] These variations in death rates are probably due to different types and levels of exposure to carcinogens, and availability of imaging services for early diagnosis. The same downward trends in mortality from all cancers was observed in men from 53 of 60 countries in women from 54 of 60 countries according to WHO data from 2000 to 2010.[24] On the other hand, this study showed that Brazil was one of the few countries where mortality from all cancers did not decrease and, according to our data, this trend persisted until (at least) 2017.

Cardiovascular diseases and cancer

This study showed that deaths from CVD and cancers corresponded to around 50% of all deaths in the period from 1996 to 2017. There was a downward trend in mortality from CVD, while mortality rates from all cancers remained unchanged. Previous study showed the same trend of



	IHD	Stroke	HF	CH	CMP	HHC
1996 All population	32	23	11	6	5	7
1996 Men	36	24	10	6	5	6
1996 Women	28	24	12	6	5	8
2017 All population	37	14	6	6	4	11
2017 Men	41	18	6	5	4	10
2017 Women	32	14	6	6	3	12

Figure 3 – *The percentage of the six main causes of cardiovascular death in the Brazilian population. CH: cerebral hemorrhage; CMP: cardiomyopathy; HF: heart failure; HHC: hypertension and hypertensive cardiopathy; IHD: ischemic heart disease.*

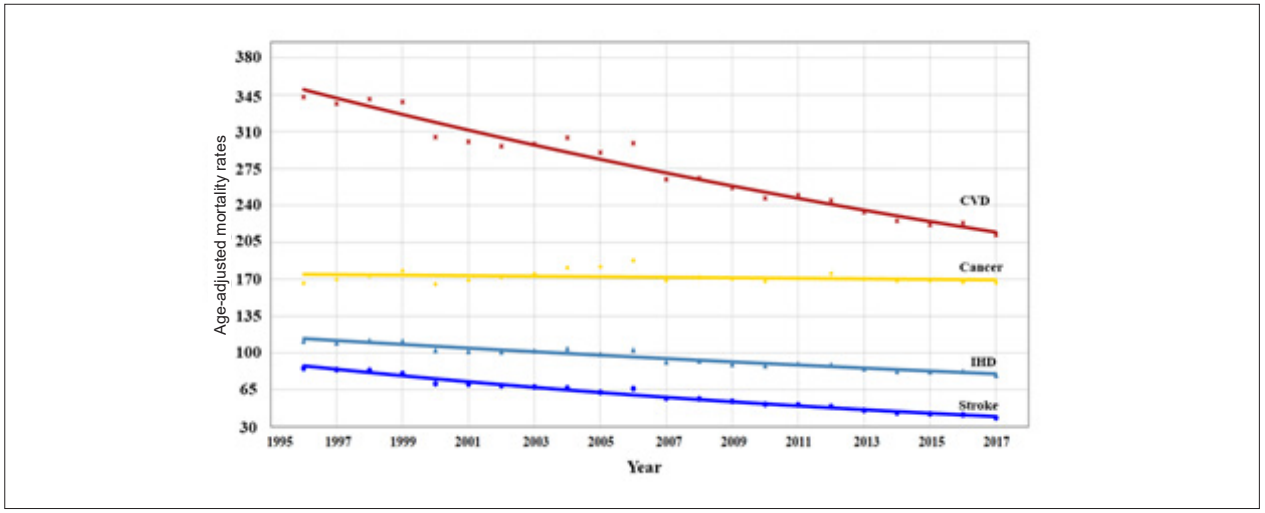


Figure 4 – *Trends in mortality rates from cardiovascular disease (CVD), ischemic heart disease (IHD), stroke, and cancer in Brazil from 1996 to 2017.*

decreasing mortality from CVD and an unchanged trend of mortality from all causes of cancer in Brazil. In more developed countries, however, in addition to the reduction in mortality from CVD, there was also a reduction in cancer mortality.[25] Likewise, a significant convergence of mortality from these diseases has been observed globally. Our data showed that CVD mortality in Brazil in 1996 was twice as high as cancer mortality, while in 2017, CVD mortality was only 22% higher than cancer mortality. However, in some developed countries, mortality from cancer was already higher than from CVD. A recent study showed that cancer mortality from 1999 to 2017 was higher than from heart disease in USA in the 45 to 64 age group.[7] The same trend has been observed in several European countries.[26] Our study also showed that since 2002, cancer mortality has been greater than the sum of death from IHD and stroke. This trend occurred earlier in women, in 1997, and later in men, in 2008. Although cancer was the main cause of death in several countries in this period, a decreasing trend in mortality from all cancers was observed in most of them, which was not observed in Brazil, where mortality rates from all types of cancer remained unchanged.

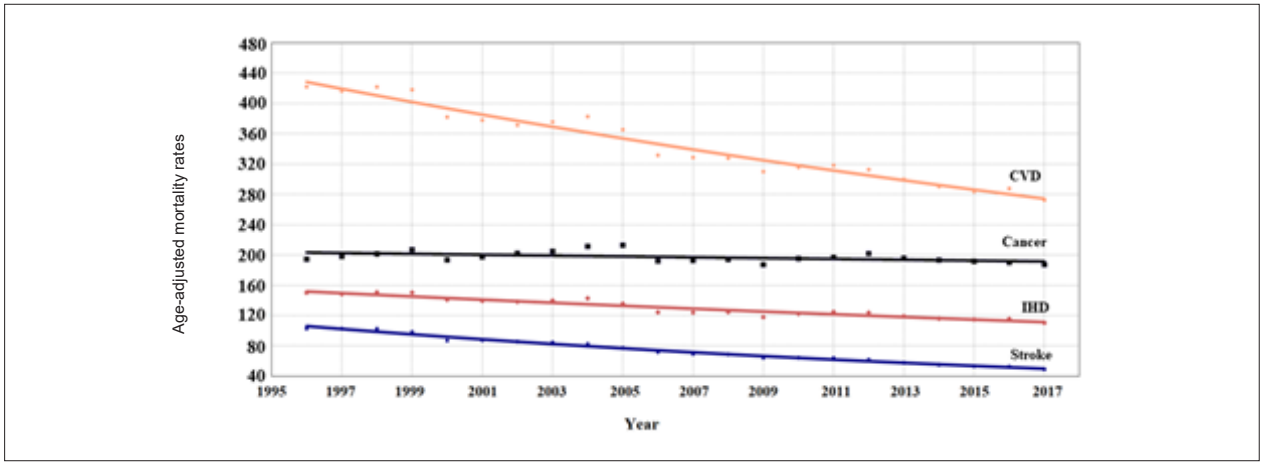


Figure 5 – *Trends in mortality rates from cardiovascular disease (CVD), ischemic heart disease (IHD), stroke, and cancer in Brazilian men from 1996 to 2017.*

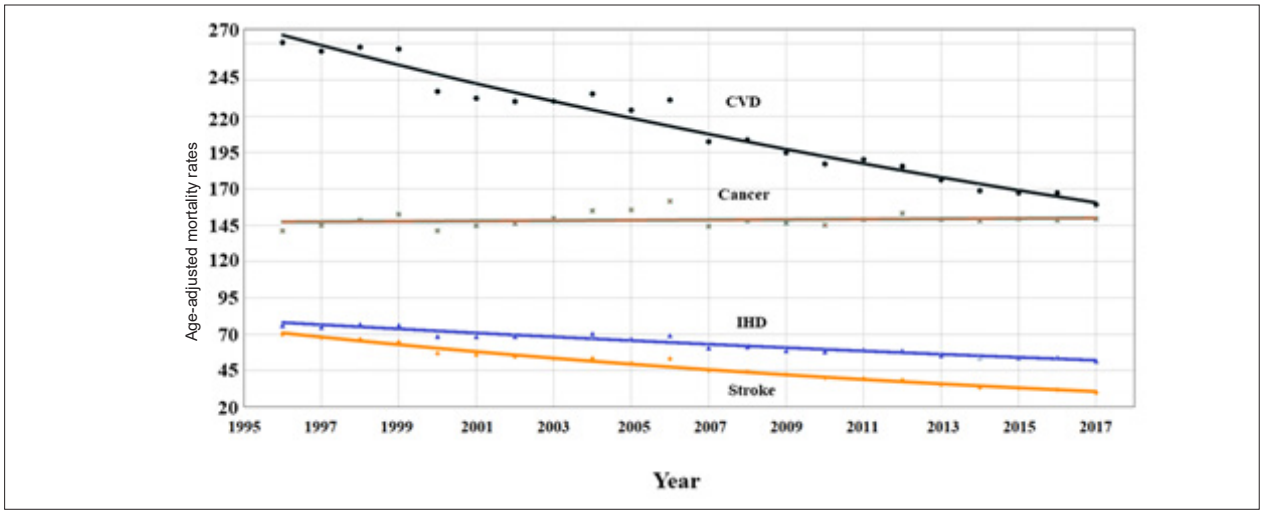


Figure 6 – *Trends in the mortality of cardiovascular disease (CVD), ischemic heart disease (IHD), stroke, and cancer in Brazilian women from 1996 to 2017.*

Study limitations

The poor quality of mortality data in Brazil, exampled by errors related to the diagnosis and accuracy of death certificates, deaths associated with unknown causes, and errors in data entry were the main limitations of the study. The number of death certificates with diagnosed based on symptoms, signs, and abnormal clinical and laboratory findings, rather than on the ICD, is an indirect indicator of limitations of data quality. Despite progressive improvements, such certificates are still significantly present in the northeast, north, and central west regions of Brazil, but much less in the south and southeast regions. Validation studies for mortality data are also not available in most states or cities in Brazil.

Conclusion

The Brazilian population has different trends in mortality rates from CVD and cancer. CVD are still the main causes of death in the country, but if the observed death rate trends continue, in a few years cancers will be the main causes of death in the Brazilian population aged 35-74 years. Therefore, primary prevention of CVD and cancers should be prioritized, by intensifying control of the main risk factors for CVD, which will also affect the incidence of new cancers, and improving the early diagnosis of cancer.

Author Contributions

Conception and design of the research, Analysis and interpretation of the data, Statistical analysis and Critical revision of the manuscript for intellectual contente: Mansur AP, Favarato D; Acquisition of data: Favarato D; Writing of the manuscript: Mansur AP.

Potential Conflict of Interest

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

Table 4 – Crude mortality rates per 100 000 population from ischemic heart disease and stroke in the general population in Brazil from 1996 to 2017

	Ischemic heart disease						Stroke					
	1996	2017	% change	AAPC(%)	99%CI		1996	2017	% change	AAPC(%)	99%CI	
35 – 39	13.29	8.07	-39	-1,7*	-2,2	-1,2	7,75	2,59	-67	-4.6*	-5.1	-4.1
40 – 44	26.61	17.66	-34	-2,1*	-2,4	-1,8	16,41	6,07	-63	-5.0*	-5.3	-4.7
45 – 49	49.47	32.99	-33	-2,1*	-2,3	-1,9	32,28	10,93	-66	-5.3*	-5.5	-5.0
50 – 54	81.50	58.58	-28	-1,9*	-2,2	-1,6	55,99	19,51	-65	-5.1*	-5.3	-4.8
55 – 59	134.79	93.00	-31	-1,7*	-2	-1,4	94,01	35,01	-63	-4.5*	-4.7	-4.3
60 – 64	211.01	151.31	-28	-1,5*	-1,7	-1,3	149,57	67,34	-55	-3.8*	-4.0	-3.6
65 – 69	307.56	223.24	-27	-1,5*	-1,6	-1,3	247,26	122,81	-50	-3.3*	-3.5	-3.1
70 – 74	443.13	326.20	-26	-1,6*	-1,8	-1,3	415,42	220,28	-47	-2.9*	-3.1	-2.7
Men												
35 – 39	18,95	11,53	-39	-1,8*	-2.3	-1.2	8,16	2,91	-64	-4.5*	-5.1	-4.0
40 – 44	39,03	25,05	-36	-2,3*	-2.7	-2.0	18,52	6,59	-64	-5.1*	-5.5	-4.8
45 – 49	70,45	46,04	-35	-2,2*	-2.5	-2.0	36,38	11,75	-68	-5.4*	-5.7	-5.0
50 – 54	117,12	84,66	-28	-1,8*	-2.1	-1.6	64,97	23,53	-64	-5.0*	-5.3	-4.7
55 – 59	188,45	134,54	-29	-1,6*	-1.9	-1.3	116,25	44,08	-62	-4.5*	-4.7	-4.2
60 – 64	287,28	212,78	-26	-1,3*	-1.6	-1.0	186,52	87,85	-53	-3.7*	-3.9	-3.5
65 – 69	403,3	307,46	-24	-1,2*	-1.4	-1.0	305,16	160,48	-47	-3.1*	-3.3	-2.8
70 – 74	556,69	439,34	-21	-1,1*	-1.3	-0.9	495,87	285,93	-42	-2.6*	-2.8	-2.4
Women												
35 – 39	7,92	4,65	-41	-1.8*	-2.5	-1.0	7,35	2,28	-69	-4.7*	-5.2	-4.1
40 – 44	14,76	10,44	-29	-1.8*	-2.1	-1.4	14,4	5,57	-61	-4.8*	-5.2	-4.5
45 – 49	29,43	20,46	-30	-1.9*	-2.2	-1.5	28,36	10,13	-64	-5.1*	-5.5	-4.7
50 – 54	47,72	34,04	-29	-1.9*	-2.3	-1.5	47,48	15,73	-67	-5.2*	-5.6	-4.8
55 – 59	85,91	54,97	-36	-1.8*	-2.5	-1.2	73,75	26,7	-64	-4.6*	-4.9	-4.3
60 – 64	143,16	96,96	-32	-1.9*	-2.1	-1.7	143,16	96,96	-32	-4.0*	-4.2	-3.8
65 – 69	224,89	152,05	-32	-1.8*	-2.1	-1.6	197,26	90,97	-54	-3.6*	-3.9	-3.3
70 – 74	346,44	236,73	-31	-2.1*	-2.3	-1.8	346,93	168,36	-51	-3.2*	-3.5	-2.9

*%change: 2017 death rate minus 1996 death rate; AAPC: average annual percentage change; CI: confidence interval; *p<0.001*

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.

Table 5 – Age-adjusted mortality rates (per 100 000 population) of the main causes of death from cancer in men and women in Brazil from 1996 to 2017

Men	1996	2017	% change	AAPC(%)	99%CI	
Lung	35.55	27.78	-22	-1.3*	-1.6	-1.1
Gastric	25.88	15.83	-39	-2.2*	-2.5	-2.0
Prostate	15.51	15.64	1	-0.2	-0.4	0.1
Esophagus	15.73	13.24	-16	-0.8*	-1.0	-0.5
Colon	6.69	9.26	38	1.5*	1.3	1.8
Women						
Breast	24.44	28.01	15	0.4*	0.2	0.6
Lung	11.50	17.80	55	1.9*	1.6	2.2
Cervix	11.22	10.91	-3	-0.9*	-1.3	-0.6
Gastric	10.22	6.95	-32	-1.6*	-1.9	-1.4
Colon	6.40	8.20	28	1.0*	0.8	1.3

%change: 2017 death rate minus 1996 death rate; AAPC: average annual percentage change; CI: confidence interval.
**p<0.001*

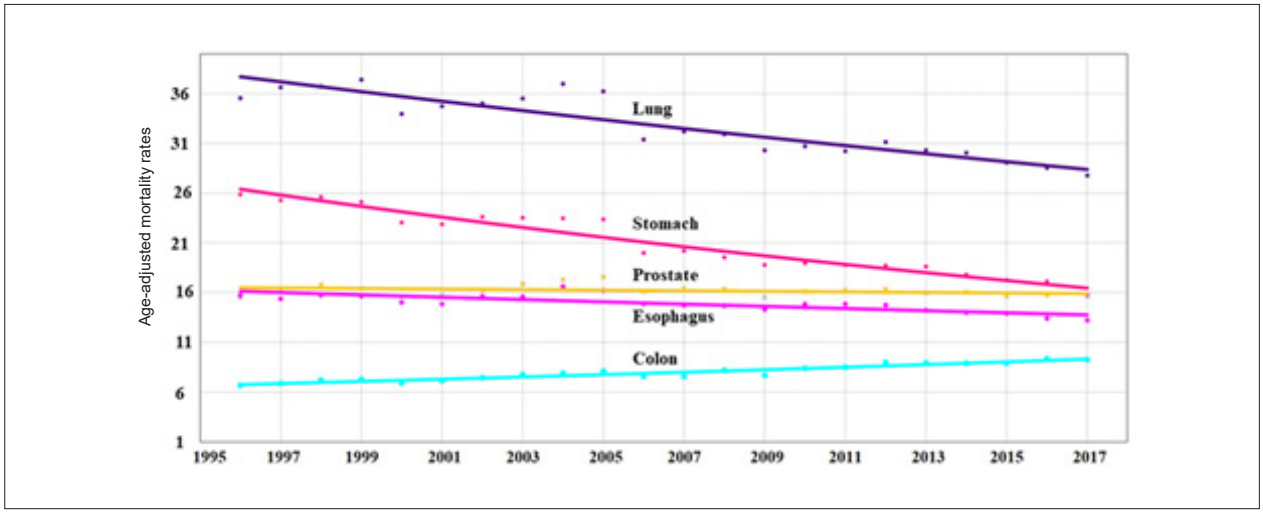


Figure 7 – *Mortality rates of the five main cause of deaths from cancer in Brazilian men from 1996 to 2017.*

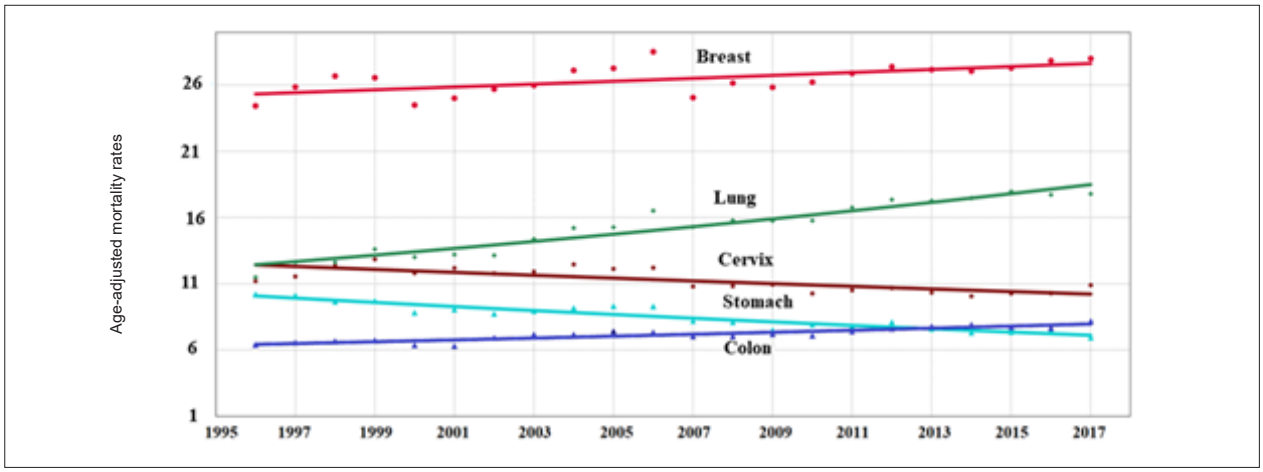


Figure 8 – *Mortality rates of the four main cause of deaths from cancer in Brazilian women from 1996 to 2017.*

References

1. Brasil. Ministério da Saúde. DATASUS. Brasília, DF: OMS/DATASUS; 2019 [citado 9 dez. 2019]. Disponível em: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sim/cnv/obt10uf.def.
2. GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1736-88.
3. World Health Organization. Noncommunicable diseases [Internet]. Geneva: WHO; 2018 [citado 9 dez. 2019]. Disponível em: https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases.
4. Mansur AP, Favarato D. Trends in mortality rate from cardiovascular disease in Brazil, 1980-2012. Arq Bras Cardiol. 2016;107(1):20-5.
5. Mansur AP, Favarato D. Mortality due to Cardiovascular Diseases in Women and Men in the Five Brazilian Regions, 1980-2012. Arq Bras Cardiol. 2016;107:137-146.
6. Curtin SC. Trends in cancer and heart disease death rates among adults aged 45-64: United States, 1999-2017. Natl Vital Stat Rep. 2019;68(5):1-9.
7. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69(1):7-34.
8. Stringhini S, Carmeli C, Jokela M, Avendaño M, Muennig P, Guida F, et al. Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1·7 million men and women. Lancet. 2017;389(10075):1229-37.
9. Rasmussen-Torvik LJ, Shay CM, Abramson JG, Friedrich CA, Nettleton JA, Prizment AE, et al. Ideal cardiovascular health is inversely associated with incident cancer: the Atherosclerosis Risk In Communities study. Circulation. 2013;127(12):1270-5.
10. Brasil. Ministério da Saúde. DATASUS. Brasília, DF: OMS/DATASUS; 2019 [citado 15 set. 2019]. Disponível em http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sim/cnv/obt10uf.def.
11. National Cancer Institute Division of Cancer Control and Population Sciences. Joinpoint regression program, version 4.7.0.0; 2019 [citado 15 set. 2019]. Disponível em: https://surveillance.cancer.gov/joinpoint/.
12. Currell G. Scientific Data Analysis [Internet]. Oxford: Oxford University Press; 2015 [citado 10 jan. 2020]. Disponível em: https://www.youtube.com/watch?v=myL_qzuLHTQ.
13. Roth GA, Johnson C, Abajobir A, Abd-Allah F, Abera SF, Abyu G, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. J Am Coll Cardiol. 2017;70(1):1-25.
14. Benjamin EJ, Muntner P, Alonso A, Bittencourt MS, Callaway CW, Carson AP, et al; American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart Disease and Stroke Statistics-2019 Update: A Report From the American Heart Association. Circulation. 2019;139(10):e56-e528.
15. Wilmot KA, O'Flaherty M, Capewell S, Ford ES, Vaccarino V. Coronary heart disease mortality declines in the United States from 1979 through 2011: Evidence for stagnation in young adults, especially women. Circulation. 2015;132(11):997-1002.
16. Nichols M, Townsend N, Scarborough P, Rayner M. Trends in age-specific coronary heart disease mortality in the European Union over three decades: 1980-2009. Eur Heart J. 2013;34(39):3017-27.
17. Ward ZJ, Bleich SN, Cradock AL, Barrett JL, Giles CM, Flax C, et al. Projected U.S. state-level prevalence of adult obesity and severe obesity. N Engl J Med. 2019;381(25):2440-50.
18. Shah NS, Lloyd-Jones DM, O'Flaherty M, Capewell S, Kershaw KN, Carnethon M, et al. Trends in cardiometabolic mortality in the United States, 1999-2017. JAMA. 2019;322(8):780-2.
19. Ribeiro AL, Duncan BB, Brant LC, Lotufo PA, Mill JG, Barreto SM. Cardiovascular health in Brazil: trends and perspectives. Circulation. 2016;133(4):422-33.
20. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394-424.
21. Ferlay J, Colombet M, Soerjomataram I, Dyba T, Randi G, Bettio M, et al. Cancer incidence and mortality patterns in Europe: Estimates for 40 countries and 25 major cancers in 2018. Eur J Cancer. 2018 Nov;103:356-87.
22. Global Burden of Disease Cancer Collaboration, Fitzmaurice C, Abate D, Abbasi N, Abbastabar H, Abd-Allah F, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2017: A Systematic Analysis for the Global Burden of Disease Study. JAMA Oncol. 2019;5(12):1749-68.

23. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30.

24. Hashim D, Boffetta P, La Vecchia C, Rota M, Bertuccio P, Malvezziet M, et al. The global decrease in cancer mortality: trends and disparities. Ann Oncol. 2016;27(5):926-33.

25. Araújo F, Gouvinhas C, Fontes F, La Vecchia C, Azevedo A, Lunet N. Trends in cardiovascular diseases and cancer mortality in 45 countries from five continents (1980-2010). Eur J Prev Cardiol. 2014;21(8):1004-17.

26. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. Eur Heart J. 2016;37(42):3232-45.

Successes and Challenges in the Management of Cardiovascular Disease in Brazil: Living Longer and Better

Bruno Fernandes Galdino,[1] David Costa Peixoto,[1] Ana Carolina Alves,[2] Bruno Ramos Nascimento,[1,3] Luisa Campos Caldeira Brant[1,3]

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

Faculdade de Medicina, Faculdade de Saúde e Ecologia Humana,[2] Belo Horizonte, MG - Brazil

Serviço de Cardiologia e Cirurgia Cardiovascular e Centro de Telessaúde, Hospital das Clínicas, Universidade Federal de Minas Gerais,[3] Belo Horizonte, MG – Brazil

Short Editorial related to the article: Cardiovascular and Cancer Death Rates in the Brazilian Population Aged 35 to 74 Years, 1996-2017

Cardiovascular diseases (CVDs) and cancer are the main causes of death in Brazil and worldwide. Considering this epidemiological relevance, the article "Mortality Rates from Cardiovascular Diseases and Cancer in the Brazilian Population aged 35 to 74 Years, 1996-2017",[1] through the analysis of mortality data from the DATASUS Vital Statistics (Mortality Information System – SIM), depicts the mortality profile of these groups of diseases, discusses their evolution between 1996 and 2017, and estimates the future contribution of these causes of death, if the trends are maintained. The main findings include the greater current contribution of CVDs to mortality in Brazil, but with a gradual reduction of their age-standardized rates. This trend did not occur for cancer mortality rates – which remain stable – so that, in a few years, cancer will become the main cause of death in the country.

CVDs and cancer, despite having different etiopathogeneses, share risk factors (RF), such as smoking, obesity, diabetes, excessive alcohol consumption and low socioeconomic status. Therefore, maintaining an optimal cardiovascular health is inversely proportional to the incidence of cancer.[2] Thus, it is important to understand the population exposure trends to these common RFs over the last decades, when lifestyle changes resulting from urbanization and population aging contributed to the high incidence and mortality of both diseases.[3] With this information in mind, Mansur and Favarato analyzed mortality data from all causes for men and women, CVD, ischemic heart disease (IHD), cerebrovascular disease (CbVD) and cancer over this 21-year period.

Proportional mortality rates from CVD (30%) and cancer (20%) accounted for half of the deaths between 1996 and 2017. During this period, the age-standardized mortality rate from CVD decreased by 38%, which is in line with the estimates of the Global Burden of Disease 2017 study published by Malta et al.,[4] which showed a decrease of 34.8% from 2000 to 2017. The GBD study tries, when processing the country's primary mortality data through models that include corrections for underreporting and redistribution of garbage codes, to minimize the limitations of SIM – such as disparities in coverage and in the proportion of ill-defined causes of death, historically higher in less developed states.[4]

The authors also observed that age-standardized CVD mortality rates are lower among women and that the decrease in mortality was more significant in this group. Martins et al.[5] considering similar findings, attributed both trends to women's greater adherence to screening and prevention of these diseases in primary health care (PHC), in addition to the hormonal protection that is known to delay mortality from CVD among women.[5]

IHD and CbVD were responsible for 57% of CVD deaths, with CbVD mortality rates showing a more pronounced reduction, possibly due to better identification, management and control of systemic arterial hypertension (SAH) in this period,[6] a risk factor more strongly related to CbVD than IHD – that is more associated with metabolic factors than CbVD, which showed unfavorable trends in the period.[7,8]

The downward pattern of CVD mortality rate in both men and women in Brazil is intrinsically related to the implementation of public policies for the control of RFs – such as those aimed at smoking control or those allowing access to SAH treatment – the implementation of urgent and emergency care system in 2003, as well as improvements and expansion of the Primary Care network in the country.[6] These measures promote healthy habits, allow for the early diagnosis and treatment of acute and chronic CVDs, in addition to the control of its determinants – the pillars of CVD treatment. Despite this relative success, it is important to note that CVD mortality rates are still high, as mentioned by Mansur and Favarato,[1] and the country still faces major challenges: the uneven reduction in mortality rates, which is lower in less developed Brazilian states and among men, the growing number of deaths due to population growth and aging, in addition to the increased prevalence of obesity and its adverse metabolic consequences.[6,8]

Regarding cancer, the study observed that there were no significant variations in the age-standardized mortality rate in the general population between 1996 and 2017. This occurred due to the 5.8% increase in mortality among women (Mean Annual Percentage Change [MAPC] =0.3%, p=0.2), despite the significant reduction of 3.7% among men (MAPC=-0.1%, p<0.001). It is important to note that, across regions of the country, large differences in mortality patterns are observed. In the North and Northeast regions,

Keywords

Successes; Challenges; Epidemiology; Cardiovascular diseases; Cancer.

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

DOI: https://doi.org/10.36660/abc.20210589

for instance, infection-related neoplasms are more usual – a common characteristic in low- and middle-income countries – while other regions of Brazil show a pattern similar to that of high-income countries, with cancer associated with aging and to chronic conditions.[9,10] Additionally, the North and Northeast regions show increasing trends in cancer mortality until 2030, while the trends are stable or decreasing in the other regions,[11] showing how higher mortality, regardless of the cause, is closely related to poverty, which acts unfavorably on several fronts: educational, nutritional, and regarding access to diagnosis and treatment.[10]

Given the abovementioned facts, a proportional increase in mortality from cancer is expected as the mortality from CVD decreases, since the causes of death are competitive. Therefore, since death is unavoidable, it is worth highlighting other information disclosed by Mansur and Favarato: the more significant reduction in mortality from all causes and, especially, from CVDs, in the younger age groups, disclosing a decrease in premature mortality in Brazil in recent decades,[11] one of the Sustainable Development Goals proposed by the World Health Organization for 2030.[12]

In short, the data from the present study show advances, but reinforce that perennial and new challenges require the implementation and renewal of public policies that promote the fight against CVDs and cancer as priorities in the health scenario in the country, so that Brazilians can live longer and better.

References

1. Mansur AP, Favarato D. Cardiovascular and Cancer Death Rates in the Brazilian Population Aged 35 to 74 Years, 1996-2017. Arq Bras Cardiol. 2021; 117(2):329-340. doi: https://doi.org/10.36660/abc.20200233
2. Rasmussen-Torvik LJ, Shay CM, Abramson JG, Friedrich CA, Nettleton JA, Prizment AE, et al. Ideal Cardiovascular Health is Inversely Associated with Incident Cancer: The Atherosclerosis Risk in Communities Study. Circulation. 2013;127(12):1270-5. doi: 10.1161/CIRCULATIONAHA.112.001183.
3. Ribeiro ALP, Duncan BB, Brant LC, Lotufo PA, Mill JG, Barreto SM. Cardiovascular Health in Brazil: Trends and Perspectives. Circulation. 2016;133(4):422-33. doi: 10.1161/CIRCULATIONAHA.114.008727.
4. Malta DC, Teixeira R, Oliveira GMM, Ribeiro ALP. Cardiovascular Disease Mortality According to the Brazilian Information System on Mortality and the Global Burden of Disease Study Estimates in Brazil, 2000-2017. Arq Bras Cardiol. 2020;115(2):152-60. doi: 10.36660/abc.20190867.
5. Martins WA, Rosa MLG, Matos RC, Silva WDS, Souza Filho EM, Jorge AJL, et al. Trends in Mortality Rates from Cardiovascular Disease and Cancer between 2000 and 2015 in the Most Populous Capital Cities of the Five Regions of Brazil. Arq Bras Cardiol. 2020;114(2):199-206. doi: 10.36660/abc.20180304.
6. Brant LCC, Nascimento BR, Passos VMA, Duncan BB, Bensenõr IJM, Malta DC, et al. Variations and Particularities in Cardiovascular Disease Mortality in Brazil and Brazilian States in 1990 and 2015: Estimates from the Global Burden of Disease. Rev Bras Epidemiol. 2017;20(Suppl 1):116-28. doi: 10.1590/1980-5497201700050010.
7. Lotufo PA, Goulart AC, Passos VMA, Satake FM, Souza MFM, França EB, et al. Cerebrovascular Disease in Brazil from 1990 to 2015: Global Burden of Disease 2015. Rev Bras Epidemiol. 2017;20(Suppl 1):129-41. doi: 10.1590/1980-5497201700050011.
8. Brant LCC, Nascimento BR, Veloso GA, Gomes CS, Polanczyk CA, Oliveira GMM, et al. Burden of Cardiovascular Diseases Attributable to Risk Factors in Brazil: Data from the Global Burden of Disease 2019. Rev Soc Bras Med Trop. 2021;2021(54). Epub ahead of print.
9. Bigoni A, Antunes JLF, Weiderpass E, Kjærheim K. Describing Mortality Trends for Major Cancer Sites in 133 Intermediate Regions of Brazil and an Ecological Study of its Causes. BMC Cancer. 2019;19(1):940. doi: 10.1186/s12885-019-6184-1.
10. Santos MO. Estimate 2018: Cancer Incidence in Brazil. Revista Brasileira de Cancerologia. 2018;64(1):119-20.
11. Barbosa IR, Souza DLB, Bernal MM, Costa ÍDCC. Cancer Mortality in Brazil: Temporal Trends and Predictions for the Year 2030. Medicine. 2015;94(16):746. doi: 10.1097/MD.0000000000000746.
12. World Health Organization. Sustainable Development Goals. The Global Health Observatory [Internet]. Geneva: World Health Organization; 2021 [cited 2021 Jul 9]. Available from: https://www.who.int/data/gho/data/themes/sustainable-development-goals/GHO/sustainable-development-goals.

Prevalence and Related Characteristics of Patients with Brugada Pattern Electrocardiogram in Santa Catarina, Brazil

Mariana Sarmento Militz,[1] Andrei de Souza Inacio,[2] Harley Miguel Wagner,[2] Aldo von Wangenheim,[2] Alexander Romeno Janner Dal Forno,[3,4] Daniel Medeiros Moreira[1,3]

Universidade do Sul de Santa Catarina,[1] Palhoça, SC - Brazil
Universidade Federal de Santa Catarina,[2] Florianópolis, SC - Brazil
Instituto de Cardiologia de Santa Catarina,[3] São José, SC - Brazil
SOS Cardio,[4] Florianópolis, SC - Brazil

Abstract

Background: **Brugada Syndrome is an inherited arrhythmogenic disorder characterized by the presence of specific electrocardiographic features with or without clinical symptoms. The patients present increased risk of sudden death due to ventricular fibrillation. The prevalence of this electrocardiographic pattern differs according to the studied region. However, epidemiological information including the Brazilian population is scarce.**

Objectives: **To assess the prevalence of the electrocardiographic pattern of Brugada syndrome and the epidemiological profile associated with it.**

Methods: **Cross-sectional study that included 846,533 ECG records of 716,973 patients from the electrocardiogram (ECG) database from the Santa Catarina Telemedicine Network over a 4-year period. All tests were 12-lead conventional ECG (without V1 and V2 in high positions). The tests revealing "Brugada Syndrome" diagnosis (Types 1 and 2) were reviewed by a cardiac electrophysiologist. The level of significance was set at $p<0.05$.**

Results: **In total, 83 patients had a pattern potentially consistent with Brugada-type pattern ECG. Of these, 33 were confirmed having Brugada-type 1, and 22 with type 2 ECG after reevaluation. The prevalence of Brugada-type 1 ECG was 4.6 per 100,000 patients. Brugada-type 1 ECG was associated with the male gender (81.8% vs. 41.5%, $p<0.001$) and a lower prevalence of obesity diagnosis (9.1% vs. 26.4%, $p=0.028$).**

Conclusions: **This study showed low prevalence of Brugada-type ECG in Southern Brazil. The presence of Brugada-type 1 ECG was associated with the male gender and lower prevalence of obesity diagnosis comparing to the general population.**

Keywords: **Brugada Syndrome; Electrocardiography/methods; Obesity; Arrythimias; Heredity; Epidemiology.**

Introduction

Brugada syndrome (BS) is an inherited arrhythmogenic disorder characterized by the presence of specific electrocardiographic features with or without clinical symptoms. The patients are mostly young adults and present an increased risk of sudden death due to ventricular fibrillation (VF).[1,2] This clinical entity was first described in 1992 when the Brugada brothers reported 8 cases of patients with idiopathic VF who had aborted sudden cardiac death. Those patients presented ECGs showing ST-segment elevation in the right precordial leads in the absence of structural heart disease, electrolyte disturbance, or ischemia.[3]

The BS belongs to a group of channelopathies caused by mutations occurring in genes that encode or regulate sodium channels in the cardiac muscle.[4] This genetic transmission pattern has an autosomal dominant characteristic with mutations of SCN5A and SCN10A genes linked to the Brugada phenotype.[4,5]

The diagnosis of BS can be made using 12-lead ECG demonstrating elevation of the J-point in the right precordial leads.[1,2] However, the true prevalence of the syndrome among the general population is complicated to estimate because some patients have a transient Brugada-type ECG.[2] It is believed that BS is responsible for 2 to 12% of all sudden deaths, and at least 20% of deaths in patients with structurally normal hearts.[1,2] Studies conducted in Asian countries have shown a higher prevalence of Brugada-type ECG compared to other regions.[6,7] On the other hand, epidemiological information including the Brazilian population is scarce. This study was carried out to identify the prevalence and related characteristics of patients with Brugada-type ECG in Santa Catarina-Brazil.

Mailing Address: Daniel Medeiros Moreira •
Instituto de Cardiologia de Santa Catarina - Rua Adolfo Donato, s/n. Postal Code 88103-901, Praia Comprida, São José, SC - Brazil
E-mail: danielmedeirosmoreira@gmail.com
Manuscript received August 12, 2019, revised manuscript June 10, 2020, accepted August 16, 2020

DOI: https://doi.org/10.36660/abc.20190542

Methods

In this study, we included 846,533 ECG records of 716,973 patients from the electrocardiogram (ECG) database from the Santa Catarina Telemedicine Network. This is an electronic tool that helps healthcare professionals to view and diagnose image tests remotely. The network is connected to primary healthcare centers and remote regions from more than 250 cities in the State of Santa Catarina, Brazil. It is estimated that the system processes more than 17,000 ECGs monthly.[8]

Eligible individuals were all the patients who underwent a twelve-lead ECG exam and had their records processed in the Santa Catarina Telemedicine Network from August 2010 to December 2015.

Most tests were performed on an outpatient basis, especially in primary healthcare units with indication for cardiovascular assessment in primary care (data not shown). All tests from our database were evaluated by a trained cardiologist and all those identified with the descriptor "Brugada syndrome" as a diagnosis were reviewed by a second cardiologist specializing in electrophysiology.

We used the Consensus Report of the *Current electrocardiographic criteria for diagnosis of Brugada pattern* as a basis for identifying the electrocardiographic pattern.[9] The ECGs were reevaluated using the following criteria: Type 1 (coved pattern) with initial ST-elevation ≥2 mm slowly descending and concave or rectilinear with respect to the isoelectric baseline, with negative symmetric T wave in V1-V2, and Type 2 (saddle back pattern) — high take-off (r`) ≥2 mm with respect to the isoelectric line and followed by ST-elevation convex with respect to the isoelectric baseline with ≥0.05 mV elevation with positive/flat T wave in V2 and T wave variable in V1.

Only the first confirmed test of each patient was considered. For comparison, we used the first test of all the other patients who underwent ECG in the same period and were not diagnosed with BS. As this is a retrospective study, without direct access to clinical data of patients, it aimed to estimate the prevalence of the electrocardiographic pattern of Brugada syndrome. However, it is not possible to determine the true prevalence of the syndrome, since those tests that were phenocopies of the Brugada syndrome, for instance,[10] cannot be ruled out. We also compared epidemiological data between the groups of tests such as age, sex and prevalence of previous diseases, including diabetes, dyslipidemia, hypertension, chronic kidney disease, coronary artery disease, Chagas disease and previous acute myocardial infarction.

Statistical Analysis

Statistical analysis was performed using the SPSS 13.0 software for Windows (SPSS Inc., Chicago, IL, USA). We used the Kolmogorov-Smirnov test to assess the normality of continuous variables: all of them had normal distribution and, then, were presented as mean and standard deviation. Categorical variables were presented by absolute numbers and percentages. The quantitative variables between the study groups were evaluated using the unpaired Student's *t* test. Fisher's exact test was used to test the association between proportions. The level of significance was set at $p<0.05$.

Results

This study included 846,533 tests from 716,973 patients. Among them, 83 patients had a pattern potentially consistent with Brugada-type ECG. We excluded 129,560 tests because they belonged to the same patients. After reassessment of the tests with BS diagnoses by an expert in electrophysiology, it was possible to confirm 55 ECGs with Brugada pattern. Of these, 33 tests were diagnosed as Brugada type 1 pattern and 22 tests as Brugada type 2 pattern. The comparison group (with no diagnosis of BS) had 716,918 patients.

Prevalence of Brugada type 1 or 2 ECG was 7.6 per 100,000 patients. Prevalence of Brugada type 1 ECG pattern and Brugada type 2 pattern were 4.6 and 3.0 per 100,000 patients, respectively.

The sample characteristics are presented in Table 1. The mean age of patients in the Brugada type 1 or 2 group was 48.0±16.0 years. There were 78.2% of males in the Brugada type 1 or 2 group and 81.1% in the Brugada type 1 group, showing a significantly higher proportion than the general population evaluated (41.5%) with $p<0.001$ for comparison.

Regarding the clinical characteristics, patients with Brugada type 1 or 2 ECG had a significantly lower mean body mass index (25.4±4.2 kg/m^2) than individuals without Brugada (27.5 ± 5.6 kg/m^2) with $p<0.001$. In addition, patients with Brugada type 1 or 2 ECG showed a greater mean height (168.0±11.0 cm) than those without Brugada (163.3±11.1 cm) with $p=0.002$. Diagnosis of obesity was significantly less prevalent among the Brugada type 1 or 2 group (7.3%) compared to general population (26.4%) with $p=0.001$. The prevalence of obesity was also lower in the Brugada type 1 group (9.1%) compared to the general population with $p=0.028$.

No patient with Brugada pattern had previous acute myocardial infarction (AMI), Chagas disease (CD), chronic obstructive pulmonary disease (COPD) or chronic renal failure (CRF). There were no significant differences in the prevalence of previous AMI, CD, COPD, CRF and history of revascularization among the study groups (Table 1).

Discussion

Our study found a low prevalence of Brugada type 1 ECG pattern among southern Brazilians (4.6 per 100,000 patients). Kamakura,[11] in a systematic literature review, showed that the prevalence of this ECG pattern varies according to the population and age group studied. The highest prevalence of Brugada type ECG is found in some Asian countries amongst young adults, ranging from 0.14 to 7.1%, with an estimated average of 0.15%.[7,12-15] In Japan, the prevalence ranges from 4 to 122 per 10,000 inhabitants.[7,12,13,16-18] However, Western countries have a lower prevalence. Studies conducted in Europe have shown that the prevalence varies from 0 to 0.61% and an average of less than 0.02% is estimated.[11,19-24] Likewise, the Brugada-type ECG has been shown to be uncommon in North America. The prevalence observed in American and Canadian surveys ranges from 0.012 to 0.07%.[25-27] In contrast, we are not aware of studies that demonstrate the prevalence of Brugada-type ECG in the Brazilian population, only case reports and a family prevalence study of BS.[28-31]

Table 1 – Demographic and clinical variables of the study population

Variables	Brugada pattern types 1 and 2 n (%) mean ± SD	Brugada pattern type 1 n (%) mean ± SD	No Brugada pattern n (%) mean ± SD	p value*	p value †
Gender					
Male	43 (78,2)	27 (81,8)	297131 (41,5)	<0,001	<0,001
Female	12 (21,8)	6 (18,2)	419603 (58,5)	-	-
Age (years)	48.0±16,0	48.0±15,5	50.0±19,6	0,431	0,568
Height (cm)	168.0±11,0	166.8±12,6	163.3±11,1	0,002	0,067
Weight (kg)	72.6±15,6	72.7±17,2	73.6±17,4	0,664	0,776
BMI (kg/cm2)	25.4±4,2	25.7±4,5	27.5±5,6	0,001	0,084
HBP	19 (34,5)	12 (36,4)	253469 (35,4)	0,994	1,000
Obesity	4 (7,3)	3 (9,1)	188961 (26,4)	0,001	0,028
DM	6 (10,9)	3 (9,1)	54732 (7,6)	0,312	0,738
Smoking	1 (1,8)	1 (3,0)	51645 (7,2)	0,185	0,730
AMI	0 (0,0)	0 (0,0)	6960 (1,0)	>0,999	>0,999
Dyslipidemia	2 (3,6)	1 (3,0)	63229 (8,8)	0,234	0,361
CAD	6 (11,0)	3 (9,1)	92999 (13,0)	0,841	0,794
CD	0 (0,0)	0 (0,0)	359 (0,1)	>0,999	>0,999
CKD	0 (0,0)	0 (0,0)	2819 (4,0)	>0,999	>0,999
COPD	0 (0,0)	0 (0,0)	8837 (1,2)	>0,999	>0,999
Revasc	1 (1,8)	1 (3,0)	4962 (6,0)	0,268	0,171

**Brugada types 1 and 2 vs. No Brugada, †Brugada 1 vs. No Brugada; SD: standard deviation; BMI: body mass index; HBP: high blood pressure; DM: Diabetes Mellitus; AMI: previous acute myocardial infarction; CAD: coronary artery disease; CD: Chagas disease; CKD: chronic kidney disease; COPD: chronic obstructive pulmonary disease; Revasc: previous revascularization.*

The prevalence found in this study is lower than data reported in the literature and may be related to a low prevalence of Brugada-type ECG among the Brazilian population. Since the BS is a genetic condition, it is possible that the genetic variations found in the study population may have influenced the prevalence of this electrocardiographic pattern. Corroborating this hypothesis, Bezzina et al.[32] demonstrated that ethnicity-related genetic polymorphisms can modulate primary disease activity causing mutations or influencing susceptibility to arrhythmia. In the same study, a haploid genetic variant consisting of six SCN5A gene-related polymorphisms was identified only in Asian subjects and was not present in white and black individuals.[32] However, more studies are needed to clarify this issue.

In addition, it is important to recognize that the wide variation of the prevalence reported in the literature may be due to the non-standardization of Brugada pattern ECG definitions used before the publication of the Brugada Syndrome Consensus Report.[1,10] Thus, it is possible that studies conducted before that year may have overestimated the prevalence of this electrocardiographic pattern. Likewise, other factors may have influenced this variation. For example, unlike Brazil, a large part of the Japanese population has access to annual health examinations, and several studies about the prevalence of Brugada-type ECG have been published.[7,12,13,18] Moreover, as previously mentioned, the BS appears to have a higher prevalence in Southeast and East Asia, so this data cannot be extrapolated to the population of Western countries.

The gender distribution found in the population of this study showed a predominance of males (81.8% in Brugada type 1). Our findings are in agreement with epidemiological data previously reported.[11] Japanese studies have shown that Brugada-type ECG has a predominance of men, comprising about 90% of all patients with this electrocardiographic pattern. Matsuo et al.,[7] in a cohort study, observed that the percentage of men with Brugada-type ECG was 84% in a population of 43% of male participants. Similarly, Tsuji et al.,[18] in a survey including 26% of male participants, found that 84% of Brugada-type ECG were observed in male patients. Sukabe et al.[16] found a 97% prevalence of Brugada-type ECG among men in a study comprising of 79% male patients. These data suggest that the prevalence is higher among males and many multicenter studies conducted in Western countries have shown similar results to ours. This indicates that the frequency of men with Brugada-type ECG in Western countries is significantly lower than the Japanese population (72–80% vs. 94–96%).[33-39]

The higher frequency of Brugada-type ECG among male individuals found in this paper, similar to the literature, has been investigated in several studies. Although genetic transmission occurs in the same proportion between men and women, the Brugada-type ECG and the clinical manifestations of the Brugada syndrome are observed around 8 to 10 times

more in men.[40-42] Di Diego et al.,[40] in an experimental study, suggested a cellular basis for this predominance using an arterial perfusion technique in a canine right ventricle preparation. They demonstrated that the transient outward current (I_{to}), which is important to the initial phase of the action potential, was higher in the right ventricular epicardium of male dogs, thus corresponding to the mechanism responsible for the male predominance of the Brugada phenotype. In addition, Shimizo et al.,[41] in a case-control study, demonstrated significantly higher testosterone levels in men with Brugada-type ECG than controls. This hormone is known to increase outward currents (I_{to}). Consequently, accentuation of the Brugada phenotype such as ST-segment elevation and subsequent VF episodes in patients with Brugada syndrome,[43] is expected. Matsuo et al.[44] reported 2 cases of asymptomatic patients with persistent Brugada-type ECG in which the electrocardiographic pattern disappeared after orchiectomy as a treatment for prostate cancer. Similarly, Yamakawa et al.[45] investigated 20,387 Japanese children and found that the prevalence of Brugada ECG is significantly lower than in the adult population. The same study, in a comparison of genders, found a male predominance that increases with puberty. In contrast, Oe et al.[46] studied 6 and 7-year-old children and found no difference in gender prevalence. These data suggest that the gender differences among patients with Brugada-type ECG occurs after adolescence. This is the period when testosterone levels also increase.

As for the clinical characteristics of this study, patients with Brugada-type 1 or 2 ECG were taller, had lower BMI and, as a consequence, less diagnosis of obesity compared to the general population. When only the Brugada type 1 pattern is analyzed, there is a non-significant trend towards higher height and lower BMI, but obesity has also been shown to be less prevalent than the general population. Likewise, Matsuo et al.,[47] in an epidemiological case control study, found lower mean BMI in individuals with Brugada pattern than controls. Shimizo et al.[41] had similar results: the study participants were all men who presented Brugada-type ECG and lower visceral fat parameters (BMI, body fat percentage and body weight) than controls. They also observed a strong inverse association between Brugada syndrome and BMI.[41] These data, compared to the present study, suggest an association between low BMI and Brugada phenotype. Their study also demonstrated that all the visceral fat parameters were inversely correlated with testosterone levels in both patients with Brugada pattern and controls.[41] It is already known that testosterone levels in obese men are lower compared to healthy men of the same age group, and the decrease in total baseline levels of this hormone is an independent predictor of increased visceral fat.[48,49] On the contrary, if weight loss and consequent decrease in visceral fat would result in an increase in testosterone levels, weight loss could be a trigger for the Brugada phenotype, similar to a febrile state.[41,50] However, this question needs further studies to be elucidated.

There are some limitations that need to be acknowledged. The sample may not show the true profile of the southern Brazilian population, since it only evaluated the electrocardiograms from the Santa Catarina Telemedicine database, represented mostly by outpatient evaluations in a primary care setting. Since this is a retrospective review of an ECG database, the clinical outcome of these patients is unknown. In addition, it was not possible to perform a new electrocardiogram with precordial leads V1 and V2 in higher positions or to perform provocative tests with sodium channel blockers in cases of diagnostic doubt.[10] Although all electrocardiograms were evaluated by trained cardiologists, only those with the descriptor "Brugada syndrome" were reevaluated by an electrophysiologist: this fact may have underestimated the prevalence of the electrocardiographic pattern of the syndrome, since ECG interpretation varies among different observers. The study was unable to identify other diagnostic criteria for Brugada syndrome, so it cannot be established whether these patients only had Brugada-type ECG or Brugada syndrome. The ECG features of patients with Brugada syndrome may fluctuate over time and not be found in only one examination. Although this may have underestimated the prevalence of Brugada-type ECG in our study, these fluctuations represent a challenge for all cross-sectional studies, and cohort studies are required to verify these data. However, the study bias does not invalidate the findings.

Conclusion

In conclusion, our study identified a low prevalence of the electrocardiographic pattern of Brugada syndrome in Santa Catarina. The related characteristics of patients with Brugada-type 1 or 2 ECG found in this study were: male gender, greater mean height, lower mean BMI values and, as a consequence, less diagnosis of obesity compared to the general population. The related characteristics of patients with only Brugada-type 1 ECG were: male gender and less obesity than the general population.

Author Contributions

Conception and design of the research, nalysis and interpretation of the data, Statistical analysis and Writing of the manuscript: Militz MS, Dal Forno ARJ, Moreira DM; Acquisition of data: Militz MS, Inacio AS, Wagner HM, von Wangenheim A, Dal Forno ARJ, Moreira DM; Critical revision of the manuscript for intellectual content: Inacio AS, Wagner HM, von Wangenheim A.

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 Universidade do Sul de Santa Catarina under the protocol number CAAE 50968815.4.0000.5369. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

References

1. Wilde AAM, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, et al. Proposed diagnostic criteria for the brugada syndrome: consensus report. Eur Heart J. 2002;23(21):1648-54.
2. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, et al. Brugada syndrome: report of the Second Consensus Conference: endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation. 2005;111(5):659-70.
3. Brugada P, Brugada J. Right bundle branch block, persistent ST segment elevation and sudden cardiac death: a distinct clinical and electrocardiographic syndrome: a multicenter report. J Am Coll Cardiol. 1992;20(6):1391-6.
4. Lei M, Huang CLH, Zhang Y. Genetic Na+ channelopathies and sinus node dysfunction. Prog Biophys Mol Biol. 2008;98(2-3):171-8.
5. Hu D, Barajas-Martínez H, Pfeiffer R, Dezi F, Pfeiffer J, Buch T, et al. Mutations in SCN10A are responsible for a large fraction of cases of brugada syndrome. J Am Coll Cardiol. 2014;64(1):66-79.
6. Nademanee K, Veerakul G, Nimmannit S, Chaowakul V, Bhuripanyo K, Likittanasombat K, et al. Arrhythmogenic marker for the sudden unexplained death syndrome in Thai men. Circulation. 1997;96(8):2595-600.
7. Matsuo K, Akahoshi M, Nakashima E, Suyama A, Seto S, Hayano M, et al. The prevalence, incidence and prognostic value of the brugada-type electrocardiogram: a population-based study of four decades. J Am Coll Cardiol. 2001;38(3):765-70.
8. Giuliano ICB, Barcellos Junior CL, Wangenheim A, Coutinho MSSA. Issuing electrocardiographic reports remotely: experience of the telemedicine network of Santa Catarina. Arq Bras Cardiol. 2012;99(5):1023-30.
9. Luna AB, Brugada J, Baranchuk A, Borggrefe M, Breithardt G, Goldwasser D, et al. Current electrocardiographic criteria for diagnosis of Brugada pattern: a consensus report. J Electrocardiol. 2012;45(5):433-42.
10. Oliveira Neto NR, Oliveira WS, Mastrocola F, Sacilotto L. Brugada phenocopy: mechanisms, diagnosis, and implications. J Electrocardiol. 2019;55:45-50.
11. Kamakura S. Epidemiology of brugada syndrome in Japan and rest of the world. J Arrhythm. 2013;29(2):52-5.
12. Miyasaka Y, Tsuji H, Yamada K, Tokunaga S, Saito D, Imuro Y, et al. Prevalence and mortality of the brugada-type electrocardiogram in one city in Japan. J Am Coll Cardiol. 2001;38(3):771-4.
13. Furuhashi M, Uno K, Tsuchihashi K, Nagahara D, Hyakukoku M, Ohtomo T, et al. Prevalence of asymptomatic ST segment elevation in right precordial leads with right bundle branch block (Brugada-type ST shift) among the general Japanese population. Heart. 2001;86(2):161-6.
14. Gervacio-Domingo G, Isidro J, Tirona J, Gabriel E, David G, Amarillo ML, et al. The Brugada type 1 electrocardiographic pattern is common among Filipinos. J Clin Epidemiol. 2008;61(10):1067-72.
15. Sidik NP, Quay CN, Loh FC, Chen LY. Prevalence of Brugada sign and syndrome in patients presenting with arrhythmic symptoms at a Heart Rhythm Clinic in Singapore. Europace. 2009;11(5):650-56.
16. Sakabe M, Fujiki A, Tani M, Nishida K, Mizumaki K, Inoue H. Proportion and prognosis of healthy people with coved or saddle-back type ST segment elevation in the right precordial leads during 10 years follow-up. Eur Heart J. 2003;24(16):1488-93.
17. Atarashi H, Ogawa S, Harumi K, Sugimoto T, Inoue H, Murayama M, et al. Three-year follow-up of patients with right bundle branch block and ST segment elevation in the right precordial leads: Japanese Registry of Brugada Syndrome. Idiopathic Ventricular Fibrillation Investigators. J Am Coll Cardiol. 2001;37(7):1916-20.
18. Tsuji H, Sato T, Morisaki K, Iwasaka T. Prognosis of subjects with Brugada-type electrocardiogram in a population of middle-aged Japanese diagnosed during a health examination. J Am Cardiol. 2008;102(5):584-7.
19. Junttila MJ, Raatikainen MJ, Karjalainen J, Kauma H, Kesaniemi YA, Huikuri HV. Prevalence and prognosis of subjects with Brugada-type ECG pattern in a young and middle-aged Finnish population. Eur Heart J. 2004;25(10):874-8.
20. Hermida JS, Lemoine JL, Aoun FB, Jarry G, Rey JL, Quiret JC. Prevalence of the Brugada Syndrome in an Apparently Healthy Population. J Am Cardiol. 2000;86(1):91-4.
21. Bozkurt A, Yas D, Seydaoglu G, Acarturk E. Frequency of Brugada-type ECG pattern (Brugada sign) in Southern Turkey. Int Heart J. 2006;47(4):541-7.
22. Letsas KP, Gavrielatos G, Efremidis M, Kounas SP, Filippatos GS, Sideris A, et al. Prevalence of Brugada sign in a Greek tertiary hospital population. Europace. 2007;9(11):1077-80.
23. Gallagher MM, Forleo GB, Behr ER, Magliano G, De Luca L, Morgia V, et al. Prevalence and significance of Brugada-type ECG in 12,012 apparently healthy European subjects. Int J Cardiol. 2008;130(1):44-8.
24. Sinner MF, Pfeufer A, Perz S, Schulze-Bahr E, Monnig G, Eckardt L, et al. Spontaneous Brugada electrocardiogram patterns are rare in the German general population: results from the KORA study. Europace. 2009;11(10):1338-44.
25. Monroe MH, Littman L. Two-year case collection of the Brugada syndrome electrocardiogram pattern at a large teaching hospital. Clin Cardiol. 2000;23(11):849-51.
26. Patel S, Anees S, Ferrick KJ. Prevalence of Brugada Pattern in an Urban Population in the United States. Pacing Clin Electrophysiol. 2009;32(6):704-8.
27. Lee C, Soni A, Tate RB, Cuddy TE. The incidence and prognosis of Brugada electrocardiographic pattern in the Manitoba follow-up study. Can J Cardiol. 2005;21(14):1286-90.
28. Migowski E, Araújo N, Siqueira L, Belo L, Maciel W, Carvalho H, et al. Family prevalence of Brugada syndrome. Rev SOCERJ. 2007;20(3):187-97.
29. Barros MAL, Fernandes HF, Barros CMAR, Motta FJN, Canalle R, Rey JÁ, et al. Brugada syndrome in a family with a high mortality rate: a case report. J Med Case Rep. 2013 Mar 18;7:78-84.
30. Leiria TL, Mantovani A, Ronsoni R, Pires LM, Kruse ML, Lima G. Brugada Syndrome After Using Cold Medicine: Is There any Relation? Rev Port Cardiol. 2013;32(5):415-7.
31. Maia IG, Soares MW, Boghossian SH, Sa R. The Brugada syndrome. Outcome of one case. Arq Bras Cardiol. 2000;74(5):442-5.
32. Bezzina CR, Shimizu W, Yang P, Koopmann T, Tanck M, Miyamoto Y, et al. Common sodium channel promoter haplotype in Asian subjects underlies variability in cardiac conduction. Circulation. 2006;113(3):338-44.
33. Probst V, Veltmann C, Eckardt L, Meregalli PG, Gaita F, Tan HL, et al. Long-term prognosis of patients diagnosed with Brugada syndrome: results from the FINGER Brugada syndrome registry. Circulation. 2010;121(5):635-43.
34. Brugada J, Brugada R, Brugada P. Determinants of sudden cardiac death in individuals with the electrocardiographic pattern of Brugada syndrome and no previous cardiac arrest. Circulation. 2003;108(25):3092-6.
35. Priori SG, Napolitano C, Gasparini M, Pappone C, Bella PD, Giordano U, et al. Natural history of brugada syndrome: insights for risk stratification and management. Circulation. 2002;105(11):1342-7.
36. Eckardt L, Probst V, Smits JP, Bahr ES, Wolpert C, Schimpf R, et al. Long-term prognosis of individuals with right precordial ST-segment-elevation Brugada syndrome. Circulation. 2005;111(3):257-63.
37. Priori SG, Gasparini M, Napolitano C, Bella DP, Ottonelli AG, Sassone B, et al. Risk stratification in Brugada syndrome: results of the PRELUDE registry. J Am Coll Cardiol. 2012;59(1):37-45.
38. Takagi M, Yokoyama Y, Aonuma K, Aihara N, Hiraoka M. Clinical characteristics and risk stratification in symptomatic and asymptomatic patients with brugada syndrome: multicenter study in Japan. J Cardiovasc Electrophysiol. 2007;18(12):1244-51.

39. Kamakura S, Ohe T, Nakazawa K, Aizawa Y, Shimizu A, Horie M, et al. Long-term prognosis of probands with Brugada-pattern ST-elevation in leads V1-V3. Circ Arrhythm Electrophysiol. 2009;2(5):495-503.

40. Di Diego JM, Cordeiro JM, Goodrow RJ, Fish JM, Zygmunt AC, Perez GJ, et al. Ionic and cellular basis for the predominance of the brugada syndrome phenotype in males. Circulation. 2002;106(15):2004-11.

41. Shimizu W, Matsuo K, Kokubo Y, Satomi K, Kurita T, Noda T, et al. Sex hormone and gender difference-role of testosterone on male preponderance in Brugada syndrome. J Cardiovasc Electrophysiol. 2007;18(4):415-21.

42. Benito B, Sarkozy A, Mont L, Henkens S, Berruezo A, Tamborero D, et al. Gender differences in clinical manifestations of Brugada syndrome. J Am Coll Cardiol. 2008;52(19):1567-73.

43. Bai CX, Kurokawa J, Tamagawa M, Nakaya H, Furukawa T. Nontranscriptional Regulation of cardiac repolarization currents by testosterone. Circulation. 2005;112(12):1701-10.

44. Matsuo K, Akahoshi M, Seto S, Yano K. Disappearance of the Brugada-type electrocardiogram after surgical castration: a role for testosterone and an explanation for the male preponderance. Pacing Clin Electrophysiol. 2003;26(7 Pt 1):1551-3.

45. Yamakawa Y, Ishikawa T, Uchino K, Mochida Y, Ebina T, Sumita S, et al. Prevalence of right bundle-branch block and right precordial ST-segment elevation (Brugada-type electrocardiogram) in Japanese children. Circulation. 2004;68(4):275-9.

46. Oe H, Takagi M, Tanaka A, Namba M, Nishibori Y, Nishida Y, et al. Prevalence and clinical course of the juveniles with Brugada-type ECG in Japanese population. Pacing Clin Electrophysiol. 2005;28(6):549-54.

47. Matsuo K, Akahoshi M, Nakashima E, Seto S, Yano K. Clinical Characteristics of Subjects with the Brugada-Type Electrocardiogram. J Cardiovasc Electrophysiol. 2004;15(6):653-7.

48. Marin P, Holmang S, Jonsson L, Sjostrom L, Kvist H, Holm G, et al. The effects of testosterone treatment on body composition and metabolism in middle-aged obese men. Int J Obes Relat Metab Disord. 1992;16(12):991-7.

49. Tsai EC, Boyko EJ, Leonetti DL, FujimotoWY. Low serum testosterone level as a predictor of increased visceral fat in Japanese-American men. Int J Obes Relat Metab Disord. 2000;24(4):485-91.

50. Mok NS, Priori SG, Napolitano C, Chan NY, Chahine M, Baroudi G. A newly characterized SCN5A mutation underlying Brugada syndrome unmasked by hyperthermia. J Cardiovasc Electrophysiol. 2003;14(4):407-11.

Brugada ECG Pattern – A Blip on the Radar for a Pontentially Life-Threatening Condition

Mirella Facin[1]

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

Short Editorial related to the article: Prevalence and Related Characteristics of Patients with Brugada Pattern Electrocardiogram in Santa Catarina, Brazil

The finding of a singular ST-segment elevation in the right precordial leads was first considered a normal variant.[1] An initial hint that this electrocardiographic (ECG) sign and sudden cardiac death (SCD) were possibly associated sprang from a case series published in 1989.[2] Three years later, Brugada *et al*. reported on eight patients who presented with right bundle branch block, persistent ST-segment elevation in V1-3, and multiple episodes of ventricular fibrillation, a new clinical and ECG syndrome that was later named after them.[3] Nowadays, Brugada syndrome (BrS) still attracts much interest due to its high prevalence in specific world regions and potential lethality in otherwise healthy young adults.[4,5]

Accounting for 4% to 12% of all cases of SCD globally and one fifth of those occurring in structurally normal hearts,[6] BrS is an autosomal dominant cardiac disease, with incomplete sex- and age-related penetrance, caused by dysfunctional sodium channels.[7,8] Although it is usually silent, BrS is clinically remarkable for male predominance, manifesting between the third and fifth decades of life.[4] Affected patients display ECG abnormalities and increased susceptibility to cardiac arrhythmias.[8] Symptoms, when present, may vary from syncope to SCD depending on the sort and duration of arrhythmic events, which often occur at rest or in vagotonic conditions.[8]

ECG findings include depolarization and repolarization abnormalities in the absence of overt structural heart disease.[4] Two distinct arrangements are currently described: type 1 and type 2 Brugada ECG pattern (BrEP).[8,9] Prominent J waves, upward ST-segment elevation ≥ 2 mm, and negative T waves in at least one standard or superior right precordial lead, the type 1 ("coved") pattern, is the BrS signature, and it is essential to diagnosis, prognosis, and risk stratification.[9] However, diagnosis of BrS is only warranted when type 1 ECG is associated with arrhythmic symptoms, family history of BrEP or SCD, and specific surrogate markers.[8] Otherwise, the individual will be considered merely a carrier of BrEP. Conversely, the type 2 ("saddle-back") pattern, an r' wave followed by elevated and convex ST-segment, although highly suspicious, is not diagnostic, and it requires supplementary investigation.[8,9]

Keywords

Brugada Syndrome; Brugada Electrocardiographic Pattern; Brugada ECG Prevalence; Standard 12-Lead ECG; Brazil

Mailing Address: Mirella Facin •
Unidade Clínica de Eletrocardiografia de Repouso - Avenida Doutor Enéas de Carvalho Aguiar, 44 - Andar AB. Postal Code 05403-900, Cerqueira César, São Paulo, SP - Brazil
E-mail: mirellafacin@incor.fm.usp.br, mirellafacin@gmail.com

DOI: https://doi.org/10.36660/abc.20210596

Identifying BrEP frequency and distribution is a cornerstone for predicting future disease load and guiding public health policies.[10] The epidemiology aspects of BrS and related ECG patterns were the primary issue in pivotal studies published in the last three decades. However, determining the burden of these disorders is not easily accomplished; on the contrary, it might pose critical caveats.

The first one regards the primarily transient nature of the underlying electrophysiological substrate, which can be modulated or induced by drugs and autonomic or metabolic conditions.[8,11] Likewise, rather than stagnant, the BrEP is dynamic and often concealed.[9] Consequently, the circumstances, duration, periodicity, and tools used for ECG monitoring may directly impact the diagnostic yield for Brugada ECG signs. As electrical abnormalities concentrate in the right ventricular outflow tract, positioning V1 and V2 in superior intercostal spaces increases the odds of recognizing a BrEP compared to a standard 12-lead ECG.

Another pitfall lies in the clinical course. Carriers of BrEP and most patients with BrS are asymptomatic.[8] They do not voluntarily seek health care facilities, and they may, therefore, be underrepresented in tertiary center cohorts. Additionally, BrEP is not specific for BrS; other conditions should be excluded, such as acute myocardial infarction, electrolyte imbalances, pulmonary embolism, and mediastinal masses.[12]

Last but not least, the frequencies of BrEP and BrS differ significantly worldwide. This wide range is likely due to the interaction between local/environmental and racial-specific/genetic aspects.[13] However, it may also reflect the heterogeneity of studies regarding type/number of research centers, sampling methods, study population characteristics and size, inclusion criteria, and screening tools. These factors result in findings that are not always generalizable. Thereby, the epidemiology of BrS and BrEP remains unknown in many parts of the globe.[14]

The first Brazilian study on BrEP was published in the current edition of Arquivos Brasileiros de Cardiologia.[15] The authors assessed the telemedicine database for written reports of standard 12-lead ECG tracings from 716,973 individuals attended in basic health units of over 250 cities in Santa Catarina, Brazil, between 2010 and 2015. In their sample, unlike most studies, type 1 (4.6/100000) was more frequent than type 2 (3.0/100000).[12,14] Interestingly, the prevalence reported therein was at least ten times lower than that estimated in Western countries and less than 1% of that described in Asia, where BrS is endemic, by studies that also used standard 12-lead ECG.[14] The study by Militz *et al*. is remarkable for its sizeable study population and extensive territorial coverage, but whether those values represent all of

Short Editorial

Santa Catarina's inhabitants and their genetic variation remains unclear.[15] Moreover, these findings cannot be extrapolated to the entire population of Brazil, a continent-sized country where each state has a unique blend of races and ethnic origins. Although sampling and diagnostic issues cannot be excluded, as most ECG tracings were not reviewed, this study was the first to assess the frequency of BrEP in Brazil. Still, more studies are needed to outline the burden of BrS and its patterns nationwide.

References

1. Osher HL, Wolff L. Electrocardiographic Pattern Simulating Acute Myocardial Injury. Am J Med Sci. 1953;226(5):541-5.
2. Martini B, Nava A, Thiene G, Buja GF, Canciani B, Scognamiglio R, et al. Ventricular Fibrillation Without Apparent Heart Disease: Description of Six Cases. Am Heart J. 1989;118(6):1203-9. doi: 10.1016/0002-8703(89)90011-2.
3. Brugada P, Brugada J. Right Bundle Branch Block, Persistent ST Segment Elevation and Sudden Cardiac Death: A Distinct Clinical and Electrocardiographic Syndrome. A multicenter report. J Am Coll Cardiol. 1992;20(6):1391-6. doi: 10.1016/0735-1097(92)90253-j 6.
4. Wilde AA, Antzelevitch C, Borggrefe M, Brugada J, Brugada R, Brugada P, et al. Proposed Diagnostic Criteria for the Brugada Syndrome: Consensus Report. Circulation. 2002;106(19):2514-9. doi: 10.1161/01.cir.0000034169.45752.4a.
5. Antzelevitch C, Brugada P, Borggrefe M, Brugada J, Brugada R, Corrado D, et al. Brugada Syndrome: Report of the Second Consensus Conference: Endorsed by the Heart Rhythm Society and the European Heart Rhythm Association. Circulation. 2005;111(5):659-70. doi: 10.1161/01.CIR.0000152479.54298.51.
6. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present Status of Brugada Syndrome: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018;72(9):1046-1059. doi: 10.1016/j.jacc.2018.06.037.
7. Antzelevitch C, Yan GX. J-Wave Syndromes: Brugada and Early Repolarization Syndromes. Heart Rhythm. 2015;12(8):1852-66. doi: 10.1016/j.hrthm.2015.04.014.
8. Priori SG, Wilde AA, Horie M, Cho Y, Behr ER, Berul C, et al. HRS/EHRA/APHRS Expert Consensus Statement on the Diagnosis and Management of Patients With Inherited Primary Arrhythmia Syndromes: Document Endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. Heart Rhythm. 2013;10(12):1932-63. doi: 10.1016/j.hrthm.2013.05.014.
9. Luna AB, Brugada J, Baranchuk A, Borggrefe M, Breithardt G, Goldwasser D, et al. Current Electrocardiographic Criteria for Diagnosis of Brugada Pattern: A Consensus Report. J Electrocardiol. 2012;45(5):433-42. doi: 10.1016/j.jelectrocard.2012.06.004.
10. Epidemiology is a Science of High Importance. Nat Commun. 2018;9(1):1703. doi: 10.1038/s41467-018-04243-3.
11. Scanavacca MI, Hachul DT. Programmed Ventricular Stimulation in the Management of Brugada Syndrome Patients. Arq Bras Cardiol. 2019;112(3):217-19. doi: 10.5935/abc.20190047.
12. Postema PG. About Brugada Syndrome and its Prevalence. Europace. 2012;14(7):925-8. doi: 10.1093/europace/eus042.
13. Quan XQ, Li S, Liu R, Zheng K, Wu XF, Tang Q. A Meta-Analytic Review of Prevalence for Brugada ECG Patterns and the Risk for Death. Medicine. 2016;95(50):e5643. doi: 10.1097/MD.0000000000005643.
14. Shi S, Barajas-Martinez H, Liu T, Sun Y, Yang B, Huang C, et al. Prevalence of Spontaneous Brugada ECG Pattern Recorded at Standard Intercostal Leads: A meta-analysis. Int J Cardiol. 2018;254:151-156. doi: 10.1016/j.ijcard.2017.11.113.
15. Militz MS, Inacio AS, Wagner HM, Wangenheim A, Dal Forno ARJ, Moreira DM. Prevalence and Related Characteristics of Patients with Brugada Pattern Electrocardiogram in Santa Catarina, Brazil. Arq Bras Cardiol. 2021; 117(2):343-349. doi: https://doi.org/10.36660/abc.20190542

Breaks in Sedentary Time and Cardiometabolic Markers in Adolescents

Natália Maria Mesquita de Lima Quirino,[1,2] Alcides Prazeres Filho,[2,3] Arthur Oliveira Barbosa,[2,3] Gerfeson Mendonça,[2,4] José Cazuza de Farias Júnior[2,3,5]

Faculdades Nova Esperança (FACENE),[1] João Pessoa, PB – Brazil

Grupo de Estudos e Pesquisas em Epidemiologia da Atividade Física (GEPEAF), João Pessoa,[2] PB – Brazil

Programa Associado de Pós-Graduação em Educação Física (UPE/UFPB),[3] João Pessoa, PB – Brazil

Centro Universitário Cesmac,[4] Maceió, AL - Brazil

Universidade Federal da Paraíba (UFPB),[5] João Pessoa, PB - Brazil

Abstract

Background: **The interruption of the time spent in sedentary behavior (breaks) has been associated with better levels of cardiometabolic indicators in the adult population, but in adolescents, further investigations are still needed to confirm these findings.**

Objectives: **To analyze the association of the number of breaks per day in sedentary behaviors with cardiometabolic markers and whether it was moderated by nutritional status and excessive time on sedentary behavior in adolescents.**

Methods: **This is a cross-sectional study of 537 adolescents (52.3% girls), aged between 10 and 14 years, enrolled in public schools in the city of João Pessoa, Paraíba state, Brazil. The number of daily breaks (>100 counts/minutes) in sedentary time was measured by Actigraph GT3X+ accelerometers. The following cardiometabolic markers were analyzed: systolic and diastolic blood pressure (mmHg), fasting blood glucose levels, total cholesterol, triglycerides, HDL-c, LDL-c (all in mg/dL) and body mass index (BMI) (kg/m²). Linear regression was used to analyze the association between the number of breaks and cardiometabolic markers and whether this association was moderated by nutritional status and excessive time in sedentary behavior. The significance level of $p<0.05$ was adopted for all analyses.**

Results: **The number of daily breaks was negatively associated with BMI (boys – ß = -0.083; 95%CI: -0.132; -0.034 and girls – ß = -0.115; 95%CI: -0.169; -0.061), but not with the remaining cardiometabolic markers. The number of breaks per day was negatively associated with BMI (ß = -0.069; 95% CI: -0.102; -0.035), but not with the other cardiometabolic markers and this association was not moderated by the adolescents' nutritional status (p=0.221), or by excessive time in sedentary behavior (p=0.176).**

Conclusions: **Including breaks in sedentary time seems to contribute to lower BMI values in adolescents.**

Keywords: **Adolescent; Sedentarism; Adiposity; Cardiometabolic Markers; Blood Arterial; Cholesterol; Glucose; Triglycerides; Sedentary Behavior.**

Introduction

It has been hypothesized that the time spent by adolescents in sedentary behavior - activities performed in a sitting, reclining position or lying down., with energy expenditure <1.5 METs[1] - may be a risk factor for unfavorable changes in cardiometabolic markers[2,3] and health-related quality of life.[4] As such, the number of studies that have analyzed the relationship between sedentary behavior and cardiometabolic markers has increased in the last decade.[5,6]

The effects of sedentary behavior on cardiometabolic markers may be related to the decreased activity of the enzyme lipoprotein lipase (LPL), caused by muscle hypotension, resulting from prolonged sitting or reclining.[7] The lower action of LPL impairs the uptake of triglycerides, glucose, insulin and the synthesis of high density lipoprotein (HDL-C).[8,9] In addition, the time spent on these behaviors is associated with a reduction in the practice of physical activities, especially those of light intensity,[10] decrease in the total daily energy expenditure,[11] increase in body fat indicators[2] and the consumption of ultra-processed foods.[2,12,13]

It is estimated that adolescents spend around 10 hours a day on sedentary behavior,[14,15] with 30.2% spending more than eight hours.[16] In this sense, the inclusion of interruptions during

Mailing Address: José Cazuza de Farias Júnior •
Universidade Federal da Paraíba, Departamento de Educação Física, Campus I, Cidade Universitária, João Pessoa, Paraíba - Bloco de Pós-Graduação de Fisioterapia e Educação Física – CCS, Grupo de Estudos e Pesquisas em Epidemiologia da Atividade Física (GEPEAF), Sala 20, Postal Code 58051–900, João Pessoa, PB - Brazil.
E-mail: jcazuzajr@hotmail.com, jcazuzajr@gmail.com
Manuscript received January 18, 2020, revised manuscript July 02, 2020, accepted August 16, 2020

DOI: https://doi.org/10.36660/abc.20200047

the time spent per day on these behaviors, called breaks, has been considered as one of the ways to minimize the harmful health effects resulting from excessive and uninterrupted exposure to sedentary behaviors.[17]

The incorporation of breaks in sedentary time reduces muscle hypotension,[18] increasing LPL activity.[19] The breaks also promote an increase in total daily energy expenditure due to an increase in the time of physical activities, especially those of light intensity,[20] which can contribute to less accumulation of body fat[21] and improvement in lipoprotein concentrations.[22]

In adults, the number of breaks per day has been associated with a reduction in postprandial glycemia,[21] lipid profile,[23] and body mass index (BMI),[24] as well as in adiposity control.[21] In adolescents, the number of studies on breaks and cardiometabolic markers is still relatively low, with divergent results.[2,5-7,15,25-28] Studies that identified significant associations between breaks and cardiometabolic markers in this population did not adjust the analyses by sleep duration and food consumption,[15, 26,28] were performed with overweight adolescents[27] or those with a family history of obesity[26] and did not assess whether this association was moderated by nutritional status[28] and/or excessive time in sedentary behavior.[15,26,28]

Another knowledge gap is whether the association between the number of breaks and cardiometabolic markers is moderated by nutritional status and/or time in sedentary behavior, considering that overweight[29,30] and excessive time in sedentary behavior[2,6,7] are associated with changes in cardiometabolic markers. Thus, the association between taking breaks during time spent in sedentary behavior and cardiometabolic markers may differ (regarding significance and/or magnitude) according to the individual's nutritional status and/or the time spent in sedentary behavior. Thus, this study analyzed the association between the number of breaks per day in sedentary behaviors and cardiometabolic markers and whether it was moderated by nutritional status and excessive time in sedentary behavior in adolescents.

Methods

This cross-sectional research analyzed data from the first year (2014) of the LONCAAFS study (Longitudinal Study on Sedentary Behavior, Physical Activity, Eating Habits and Adolescent Health). The reference population consisted of adolescents of both genders, aged 10 to 14 years, enrolled in 6th grade at public schools in João Pessoa, Paraíba state, Northeastern Brazil. The LONCAAFS study was approved by the Human Research Ethics Committee of the Health Sciences Center at Universidade Federal da Paraíba (Protocol 240/13).

In this study, we analyzed data from a subsample of adolescents from the LONCAAFS study, which used accelerometers and underwent a blood test. This choice was made due to the number of accelerometers available (n = 64), the time available for data collection (school year) and lack of financial resources. The distribution of the sample and subsample in the geographic region of the municipality and the number of students enrolled were similar to that observed in the reference population. Information on sample selection and calculation is presented in details in Figure 1.

Data were collected between February and June and from August to December 2014, by a trained team. A questionnaire in the form of a face-to-face interview was applied to collect the following sociodemographic data: gender (male and female); age, skin color (brown; black; white; yellow; indigenous, reclassified as white and non-white); socioeconomic class [Brazilian Association of Research Companies (ABEP) criteria, which classifies families into classes A1, A2, B1, B2, C1, C2, D and E, later reclassified as class A/B (higher class) and C/D/E (lower class)][31] and mother's level of schooling (incomplete elementary school, complete elementary school, complete high school and higher education).

The hours of sleep were measured by the following question: "on weekdays and on the weekend, what time do you go to sleep and what time do you wake up?". Daily hours of sleep were determined as follows: the difference between bed and wake times during the week multiplied by five, added to the difference between these times on the weekend, multiplied by two. This result was divided by seven in order to obtain the average weighted number of hours of sleep per day. This question showed a high level of reproducibility (intraclass correlation coefficient – ICC = 0.91; 95% CI: 0.88 – 0.93).

Food intake was based on a 24-hour dietary recall.[32] The adolescents recorded the food items and beverages they had consumed on the day before the interview, as well as the weight and food preparation methods used. Thirty percent of the sample was replicated to increase the accuracy of the estimated food intake.[33] The data were tabulated in the Virtual Nutri software and the total calorie value was analyzed using the equation created by the Food and Nutrition Board of Washington.[34] In this study we used lipid and saturated fat (grams), cholesterol (mg), sodium (mg) and fiber (g) values.

BMI was measured with a digital balance, accurate to 100 grams and height was measured with a portable stadiometer. The measures were taken in triplicate by the same rater and the average value was used. Nutritional status was determined by the BMI (BMI = weight [kg] /height [m]^2) and classified according to the criteria of the World Health Organization (WHO).[35]

The blood samples were collected in the morning by nursing technicians and all the adolescents fasted for at least 12 hours before the collection. Levels of glucose (mg/dL), triglycerides (mg/dL), total cholesterol (mg/dL) and high-density lipoprotein – HDL-c (mg/dL) were determined using a Labmax 240 premium automatic biochemical analyzer (Labtest) and the turbidimetry method. Low-density lipoprotein (LDL-c) was estimated by the Friedewald, Levy and Fredrickson equation.[36]

Blood pressure was measured in the right arm using an Omron HEM – 7200 automatic monitor, at a single visit, with adolescents in the sitting position, after a five-minute rest. This instrument showed satisfactory levels of validity in a sample of adolescents with an age range similar to the present study.[37] Three measurements were obtained (systolic– intraclass correlation coefficient – ICC = 0.90; 95%CI: 0.89 – 0.91 and diastolic pressure – ICC = 0.80; 95%CI: 0.78 – 0.82), with a one-minute interval between them and the average value was used as the final result.

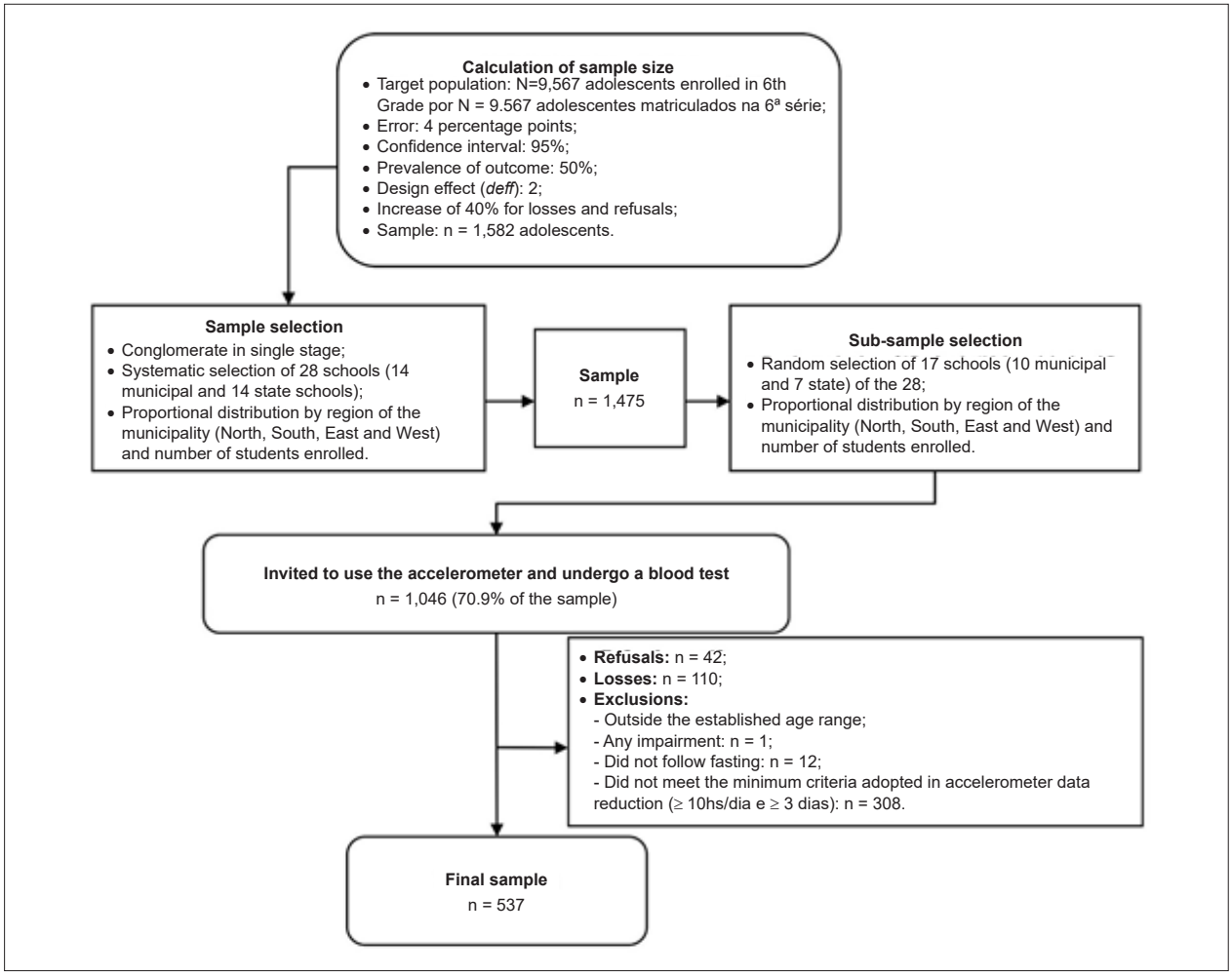


Figure 1 – *Flowchart of the study sampling process*

Time spent on sedentary behavior and moderate to vigorous physical activities and the number of breaks were measured by Actigraph GT3X+ accelerometers. The adolescents were instructed to use the accelerometer for seven consecutive days, attached to the right side of their waist by an elastic belt, removing it only when sleeping, bathing, and engaging in aquatic activities or martial arts involving falls. The accelerometer data were reduced using the ActiLife 6.12 program, adopting the following criteria:[38] A 15-second epoch (reintegrated to 60 seconds); nonuse time ≥ 60 consecutive minutes of counts equal to zero; used for at least 10 hours a day for three or more days, including at least one weekend.

Sedentary behavior and moderate to vigorous physical activity duration were determined based on the thresholds of Evenson et al.:[38] ≤ 100 and > 2,295 counts/minute, respectively. A break was operationally defined as the number of times in which the accelerometer recorded 100 counts or more for at least one minute.[39]

The number of daily breaks was determined as follows: average number of daily breaks during the week (Monday to Friday), multiplied by five, and on weekends (Saturday and Sunday), multiplied by two, dividing the sum of these values by seven. This procedure was applied to estimate the weighted mean of time spent in moderate to vigorous physical activity and sedentary behavior.

The simultaneous exposure to sedentary behavior and the daily number of breaks was operationalized as follows: a) time in sedentary behavior categorized as <8 hours/day and ≥8 hours/day (excessive time in sedentary behavior) - this cutoff point was adopted because it was associated with worse cardiometabolic health indicators in adults[40] and there is no well-established cutoff point for adolescents; b) number of breaks per day as <100 breaks/day and ≥100 breaks/day. This classification was established according to ROC [Receiver Operating Characteristic] curves, considering that there is no defined cutoff point for the number of breaks that demonstrate greater risk or protection regarding cardiometabolic health and the fact that the amount of 100 daily breaks showed more balanced values of sensitivity and specificity. Based on this, four groups of adolescents were created: 1) ≥ 8 hours of sedentary behavior and <100 breaks/day; 2) ≥ 8 hours of sedentary behavior and ≥ 100 breaks/day; 3) <8 hours of

sedentary behavior and <100 breaks/day and; 4) <8 hours of sedentary behavior and ≥ 100 breaks/day.

Adolescents who did not provide written informed consent or were absent from school on at least three data collection visits were considered sample losses. The exclusion criteria comprised adolescents outside the established age range (younger than 10 and older than 14 years), any impairment that hindered or limited physical activity and/or prevented them from completing the questionnaire; individuals who did not meet the minimum criteria adopted for accelerometer data reduction and those who did not fast for at least 12 hours.

Data analysis

To describe the quantitative variables, mean and standard deviation were used for variables with a normal distribution, and median and interquartile range for those that did not have a normal distribution, and absolute (n) and relative (%) frequencies for qualitative ones. The Kolmogorov-Smirnov test was used to verify whether the data showed a normal distribution. The chi-square test was used for the qualitative variables, and for the quantitative ones, Student's *t* test for independent samples (variables with normal distribution) and the Mann-Whitney U test (variables with non-normal distribution) were used to compare the variables between the included adolescents and those excluded from the analysis.

Simple and multiple linear regression was used to analyze the associations between the number of daily breaks in sedentary behavior and cardiometabolic markers and whether they were moderated by the nutritional status and excessive time in sedentary behavior. The analysis models were created for each dependent variable: levels of glucose [mg/dL]; total cholesterol [mg/dL]; triglycerides [mg/dL]; HDL-c [mg/dL], LDL-c [mg/dL]; systolic [mmHg] and diastolic [mmHg] blood pressure and BMI (kg/m^2).

The covariables analyzed were: gender (male = 0 and female = 1); age (in years); socioeconomic class (A / B = 0 and C / D / E = 1); skin color (white = 0 and not-white = 1); mother's level of schooling (incomplete elementary school = 0, complete elementary school = 1 and complete high school or higher = 2); hours of sleep (hours / day); consumption of lipids (g), total saturated fats (g), cholesterol (mg), sodium (mg) and fibers (g); time using the accelerometer (minutes/day) and physical activity of moderate-vigorous intensity (minutes/day) and sedentary behavior (minutes / day) and BMI, except when this variable was treated as a cardiometabolic marker in the model.

The selection method for entering the variables in the adjusted model was the Forward method, and variables that contributed to the reduction in the residual values, increased the adjusted R^2 value of the model, modified the values of the beta coefficients of the regression of the model by at least 10% of the variable number of breaks per day remained in the model. The fit quality of the models was assessed based on the values of the variance inflation factor. When assessing the fit quality of the models, the values of the variance inflation factor - VIF - were considered (values <5 indicated absence of multicollinearity), with residuals in graph form and homogeneity of variances (Cook-Weisberg test, p≥0.05 indicates the presence of homoscedasticity).

To test the possible moderation of BMI and sedentary behavior in the association between number of breaks per day and cardiometabolic markers, the following interaction terms were created: a) number of breaks/day*sedentary behavior (<8 hours and ≥8 hours); b) number of breaks/day*BMI (without overweight and with overweight). These terms were included in the adjusted models and considered as a present interaction when the p value was <0.05. In this case, the models will be treated separately according to the classification of sedentary behavior (<8 hours and ≥8 hours) and BMI (without overweight and with overweight).

The Wald test was used to compare the mean values of each cardiometabolic marker between combined exposure to sedentary behavior (<8 hours and ≥8 hours) and daily number of breaks (<100 breaks / day and ≥100 breaks / day). In this analysis, the means of each cardiometabolic marker adjusted by the same covariables of the regression models were considered. Stata 14.0 software was used and the significance level was set at p<0.05.

Results

The data of 537 adolescents, aged 10 to 14 years were analyzed (losses, refusals and exclusions totaled 509 cases, 48.6% of those invited to participate) – Figure 1. The *a posteriori* calculation indicated that with an effect size equal to or greater than 0.05; alpha (α) of 5%; and up to 12 predictors in the model, the sample of the present study had a power equal to 86%.

There was no significant difference (p≥0.05) for the variables gender, age group, socioeconomic class, mother's level of schooling and nutritional status between the sample and subsample of adolescents (data not shown in table). When comparing the characteristics of the adolescents included and excluded from the analyses, there was a higher proportion of adolescents between 12 and 14 years of age, mothers with a lower level of education, with lower values of breaks per day, time in sedentary behavior, less consumption of saturated fat, higher consumption of lipids and sodium in adolescents who were excluded from the analyses. No significant differences were identified for the other variables (p≥0.05) - Table 1.

The majority of the subjects were girls, aged 10 to 11 years, with non-white skin color, belonging to socioeconomic class C/D/E, whose mothers had at least completed elementary education and a little more than one-third were overweight. The time of physical activity, sedentary behavior and number of breaks the adolescents had was 29.1; 451.0 and 100.3, respectively (Table 1).

In the simple model, there was a significant association between the average number of breaks per day and LDL-c levels (p = 0.030), systolic blood pressure (p = 0.006) and BMI (p <0.001). In the adjusted analysis, only an association between the average number of breaks per day and the BMI (p <0.001) remained statistically significant. Sedentary behavior and BMI did not moderate the association between the number of breaks per day and cardiometabolic markers (Table 2). The final models achieved good quality of fit: absence of multicollinearity (VIF between 1.03 and 3.39),

Table 1 – Comparison of the descriptions of sociodemographic characteristics, nutritional status, food consumption, cardiometabolic markers, physical activity, sedentary behavior and number of breaks in the adolescents included and excluded from the analysis, João Pessoa, Paraíba, 2014

Variables	Included in the analyses (n = 537)		Excluded from the analyses (n = 472)		p*
	n	%	n	%	
Gender					0.281
Male	256	47.7	209	44.3	
Female	281	52.3	263	55.7	
Age					<0.001
10-11 (years)	344	64.1	230	51.3	
12-14 (years)	193	35.9	242	48.7	
Socioeconomic class					0.614
A/B	170	36.3	144	34.7	
C/D/E	298	63.7	271	65.3	
Skin color§					0.352
White	16	20.8	87	18.6	
Non-white	61	79.2	382	81.4	
Mother's level of schooling//					0.010
Incomplete elementary school	148	33.5	166	41.9	
Elementary school	130	29.4	119	30.1	
Complete high school and higher education	164	37.1	111	28.0	
Body mass index (BMI)					0.085
Underweight	14	2.6	14	3.0	
Normal weight	326	61.4	321	68.6	
Overweight	115	21.7	83	17.7	
Obesity	76	14.3	50	10.7	
Exposure to sedentary behavior					
<8 hours/day	343	63.9	192	66.9	0.386
≥8 hours/day	194	36.1	95	33.1	
	n	**Mean**	**SD**	**Mean**	**SD**	**p†**
Behavior variables						
Sleep hours (hours/day)§	536	9.7	1.6	9.6	1.6	0.871
Numbers of breaks (number/day)¶	537	100.3	91.5-108.3	92.0	82.5-104.0	<0.001‡
Physical activity (minutes/day)¶	537	29.1	17.9-45.1	30.5	16.5- 47.0	0.710‡
Sedentary behavior (minutes/day)¶	537	451.0	392.7-513.1	432.8	377.0-500.7	0.022‡
Accelerometer usage (minutes/day)	537	855.3	94.9	816.0	109.7	<0.001
Food intake						
Lipid (g)	528	71.4	45.4	77.7	51.5	0.044
Total saturated fat (g)¶	528	15.0	8.0-23.0	17.0	10.0-26.0	0.001‡
Sodium (mg)¶	528	2.055.5	1.420.5-2.852.0	2.161.0	1.534.0-3.053.0	0.028‡
Fibers (g)	528	23.1	14.2	24.3	14.4	0.198
Cholesterol (mg)	528	176.8	190.4	188.5	240.2	0.397
Cardiometabolic markers						
BMI (kg/m^2)	531	19.5	4.0	19.5	3.6	0.410
SBP (mmHg)	537	105.8	9.5	105.2	8.6	0.321
DBP (mmHg)	537	62.4	7.0	61.9	6.9	0.318
Glucose (mg/dL)	537	91.1	10.2	91.4	23.1	0.819
Cholesterol (mg/dL)§	536	159.4	31.7	158.1	32.1	0.580
Triglycerides (mg/dL) ¶	534	75.0	56-102	73.0	54-98	0.516‡
HDL (mg/dL)§	536	43.9	9.5	43.4	9.3	0.463
LDL (mg/dL)§	536	98.3	28.2	98.2	28.5	0.945

*SD: standard deviation; *: chi-square test; †: Student's T for independent variables; ‡: Mann-Whitney U test; §: Variables with fewer losses (n = 1); //: Variable with more losses (n = 101); ¶: Data presented as median and interquartile range. BMI: body mass index.*

Table 2 – Crude and adjusted linear regression for the association between the average number of breaks per day and cardiometabolic markers in adolescents from João Pessoa, Paraíba, 2014

Variables	Crude			Adjusted †			Sedentary behavior interaction term ‡			BMI interaction term§		
	ß	(95%CI)	p	ß	(95%CI)	p	ß	(95%CI)	p	ß	(95%CI)	p
Glucose (mg/dL)	0.011	-0.052; 0.073	0.737	-0.039	-0.138; 0.061	0.446	-0.021	-0.050; 0.009	0.176	-0.003	-0.037; 0.031	0.865
Cholesterol (mg/dL)	-0.181	-0.375; 0.013	0.067	-0.042	-0.336; 0.251	0.778	0.037	-0.051; 0.126	0.404	-0.046	-0.146; 0.055	0.371
Triglycerides (mg/dL)	-0.001	-0.004; 0.002	0.539	0.000	-0.004; 0.005	0.861	0.001	-0.001; 0.002	0.285	0.001	-0.001; 0.002	0.248
HDL-c (mg/dL)	0.040	-0.018; 0.099	0.174	-0.016	-0.104; 0.073	0.729	-0.013	-0.041; 0.014	0.341	0.005	-0.027; 0.036	0.761
LDL-c (mg/dL)	-0.190	-0.362; -0.018	0.030	0.019	-0.238; 0.277	0.882	0.021	-0.058; 0.101	0.598	-0.057	-0.149; 0.034	0.221
SBP (mmHg)	-0.081	-0.139; -0.023	0.006	-0.011	-0.090; 0.068	0.778	0.017	-0.008; 0.041	0.176	-0.005	-0.033; 0.023	0.710
DPB (mmHg)	-0.029	-0.072; 0.014	0.184	-0.026	-0.088; 0.037	0.421	0.008	-0.011; 0.027	0.387	-0.004	-0.025; 0.018	0.739
BMI (kg/m^2)	-0.051	-0.075; -0.026	0.000	-0.069	-0.102; -0.035	0.000	-0.004	-0.014; 0.006	0.440	--	--	--

ß: beta coefficient; 95% CI: 95% confidence interval; HDL-c: high density lipoprotein; LDL-c: low density lipoprotein; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; †: Model adjusted for gender, age, skin color, socioeconomic class, mother's level of education, hours of sleep (hours/day), fiber intake (g), lipids (g), saturated fat (g), cholesterol (mg), sodium (mg), time of accelerometer usage (min/day), total moderate to vigorous physical activity (min/day), total sedentary behavior (min/day) and BMI (kg/m^2), except when it is treated as a dependent variable; ‡: Adjusted model + interaction term between sedentary behavior (<8 hours/day vs. ≥ 8 hours/day) and number of breaks/day; §: Adjusted model + interaction term between BMI (kg/m^2) and number of breaks/day.

presence of homoscedasticity (Cook-Weisberg test with *p* values ranging from 0.054 to 0.335) and normal distribution in the regression residuals.

The results of the Wald test indicated that there were no significant differences in the mean values of cardiometabolic markers between adolescents exposed to ≥ 8 hours of sedentary behavior and <100 breaks / day, ≥ 8 hours of sedentary behavior and ≥ 100 breaks / day, <8 hours of sedentary behavior and <100 breaks / day and <8 hours of sedentary behavior and ≥ 100 breaks / day (Figures 2 and 3).

Discussion

The results of the present study indicated that the adolescents with the highest number of breaks during sedentary time obtained the lowest BMI values. However, associations with the remaining cardiometabolic markers were not significant and not moderated by the adolescents' nutritional status.

Studies with adults have demonstrated that a larger number of breaks is associated with fewer harmful effects on cardiometabolic health caused by sedentary behavior.[41] However, in adolescents, it has been associated only with body fat indicators.[2,6] The absence of an association between breaks and cardiometabolic markers may be related to the fact that a significant part of the time adolescents spend on sedentary behavior is accumulated in blocks of up to five minutes.[1,14,16] Short sedentary time blocks may minimize the reduced LPL (lipase lipoprotein) enzyme activity and contribute to increased energy expenditure. These two factors are related to the decline in blood glucose and triglycerides and increase in HDL-c levels.[42]

The excessive time in sedentary behavior did not moderate the association between the number of breaks and cardiometabolic markers. An additional analysis showed that more than 80% of the adolescents' sedentary time in the present study was accumulated in intervals of less than 10 minutes, even in those who showed excessive time in sedentary behavior (data not shown in the table). Therefore, it is possible that the benefits of including breaks on cardiometabolic markers are observed in adolescents exposed to long and uninterrupted periods of sedentary behavior.

Some experimental studies have shown that including breaks (moderate to vigorous 3-minute breaks every half hour during three hours of sedentary behavior) reduced insulin, C-peptide[27,43] and glucose levels.[43] However, this result was not confirmed by Saunders et al.[1] (mild intensity 2-minute breaks every 20 minutes during eight hours of sedentary behavior). The inconsistent results of these studies do not support the hypothesis that the benefits of including breaks occurred in adolescents who spent prolonged periods of time in sedentary behavior.

The possible lower LPL response to the hypotensive effect of sedentary behavior in adolescents and their greater capacity in maintaining cardiometabolic markers close to normal values (homeostasis), when compared to adults, may be other factors that can explain the absence of an association between breaks and cardiometabolic markers in the latter group.

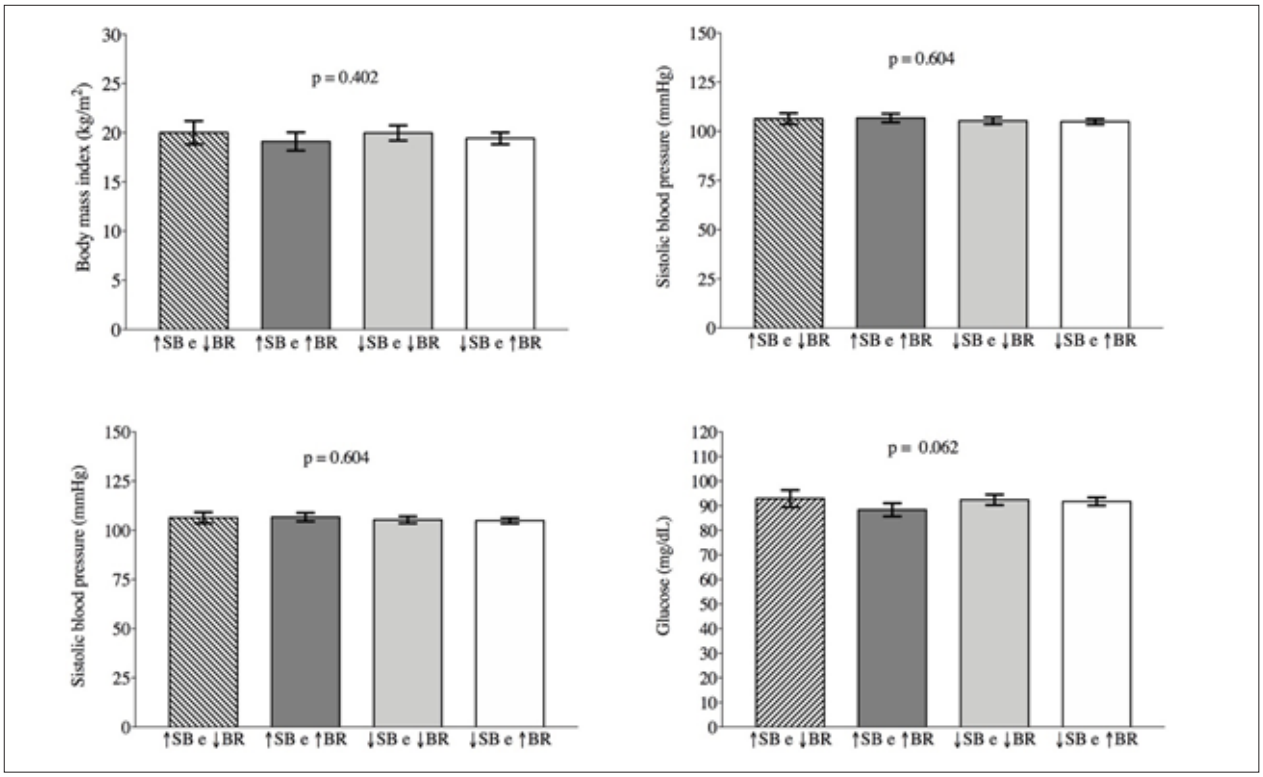


Figure 2 – *Comparison of the mean values of BMI, systolic and diastolic blood pressure and glucose between combined exposure to sedentary behavior (SB) and breaks (BR) in adolescents, João Pessoa, Paraíba, 2014. ↑ SB = ≥ 8 hours/day; ↓ SB = <8 hours/day; ↑ BR = ≥ 100 breaks/day e; ↓ BR = <100 breaks/day.*

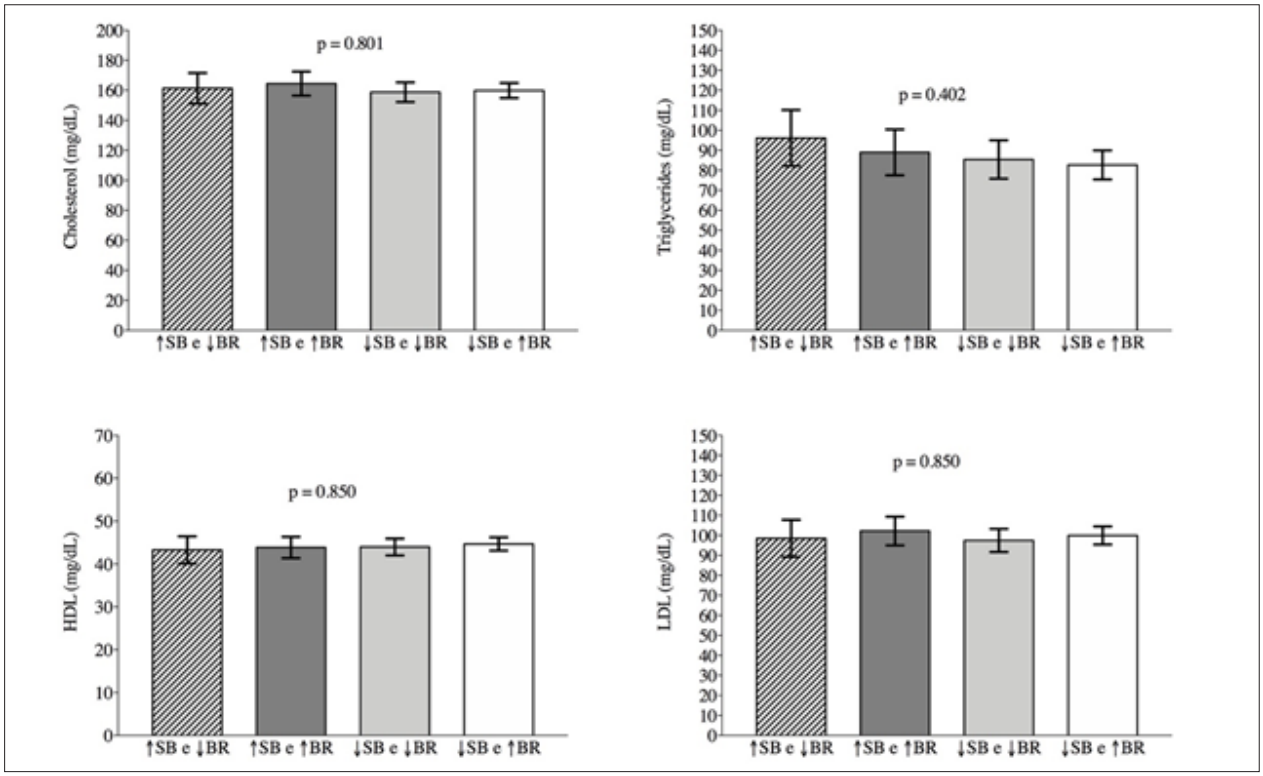


Figure 3 – *Comparison of the average values of cholesterol, triglycerides, HDL and LDL between the combined exposure to sedentary behavior (SB) and breaks (BR) in adolescents, João Pessoa, Paraíba, 2014. ↑ CS = ≥ 8 hours/day; ↓ CS = <8 hours/day; ↑ BR = ≥ 100 breaks/day e; ↓ BR = <100 breaks/day.*

In the present study, adolescents who took more breaks had lower BMI values, reinforcing the findings of other studies.[2,6] In terms of clinical relevance, the effect of breaks on BMI showed a low magnitude (for each performed break, a decrease of 0.069 kg/m^2 in BMI is estimated - effect size = 0.076). Despite this fact, the inclusion of breaks can be an easily implemented practice in the adolescents' life context, and may be one of several actions to be used in interventions aimed at reducing and/or controlling the BMI.

Moreover, breaks during sitting time tends to promote greater energy expenditure, due to the increase in physical activity. In a study with adults, Júdice et al.[15] observed that a break resulted in an average increase of 1.49 kcal/min in energy expenditure when compared to remaining in the standing position. In adolescents, since breaks may result in energy expenditure similar to that of adults, taking 100 breaks a day would be the equivalent to having a 30-minute walk at moderate intensity.[44] It has been found that more prolonged sedentary behavior is related to fewer leisure physical activity breaks[45] and greater consumption of sweets, soft drinks and industrialized/ultraprocessed foods.[46] As such, adolescents who had more daily breaks could engage in more prolonged leisure physical activity and had a lower intake of these food items. Finally, since this is a cross-sectional study, we cannot exclude the possibility that adolescents with a higher BMI would exhibit more spontaneous movement throughout the day, resulting in fewer breaks in sedentary behavior.

The following are strong points of this study: 1) data were collected from a representative sample of 6th grade-schoolchildren from public schools in a city located in Northeastern Brazil and exhibited sufficient power to test the study hypotheses; different cardiometabolic markers were analyzed and 2) important confounding factors were considered regarding the relationship between sedentary behavior and cardiometabolic markers (physical activity, hours of sleep and food intake).

The following were study limitations: not measuring the adolescents' degree of sexual maturation , a factor that can influence cardiometabolic markers[47,48] and some types of sedentary behavior;[49] reinstating the epoch accelerometer data from 15 to 60 seconds, which could have underestimated sedentary behavior time[50] and the magnitudes of the associations and the measurement of breaks during sedentary behavior using an accelerometer that measures body acceleration and not postural variation (sitting, reclining, standing).[51]

Conclusion

Adolescents who had more breaks per day during time in sedentary behavior had lower mean values of BMI but there were no differences regarding the values of the other biochemical cardiometabolic markers (levels of glucose, triglycerides, HDL-c, LDL-c, total cholesterol and blood pressure values), regardless of their nutritional status and excessive exposure to sedentary behavior.

Acknowledgment

To the National Council for Scientific and Technological Development (CNPq) and the Foundation for the Support of Research of the State of Paraíba (FAPESQPB) for the financing granted to carry out the research.

Author Contributions

Conception and design of the research: Lima NMM, Farias Júnior JC; Acquisition of data: Lima NMM, Prazeres Filho A, Barbosa AO, Farias Júnior JC; Analysis and interpretation of the data and Statistical analysis: Prazeres Filho A, Barbosa AO, Farias Júnior JC; Obtaining financing: Farias Júnior JC; Writing of the manuscript: Lima NMM, Prazeres Filho A, Barbosa AO, Mendonça G, Farias Júnior JC; Critical revision of the manuscript for intellectual content: Mendonça G, Farias Júnior JC.

Potential Conflict of Interest

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

Sources of Funding

This study was partially funded by Conselho Nacional de Desenvolvimento Cientifico e Tecnológico – CNPq e Fundação de Apoio a Pesquisa - FAPESQ do Estado da Paraíba.

Study Association

This article is part of the thesis of master submitted by Natália Maria Mesquita de Lima Quirino, from Universidade Federal da Paraíba (UFPB).

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Centro de Ciências da Saúde - UFPB under the protocol number 240/13 - CAAE: 15268213.0.0000.5188. 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. Saunders TJ, Chaput J-P, Goldfield GS, Colley RC, Kenny GP, Doucet E, et al. Prolonged sitting and markers of cardiometabolic disease risk in children and youth: a randomized crossover study. Metabolism. 2013; 62(10):1423-8.
2. Carson V, Hunter S, Kuzik N, Gray CE, Poitras VJ, Chaput J-P, et al. Systematic review of sedentary behaviour and health indicators in school-aged children and youth: an update. Appl Physiol Nutr Me. 2016; 41(6):S240-S65.
3. Vasankari V, Husu P, Vähä-Ypyä H, Suni J, Tokola K, Halonen J, et al. Association of objectively measured sedentary behaviour and physical activity with cardiovascular disease risk. Eur J Prev Cardiol. 2017; 24(12):1311-8.
4. Wu XY, Han LH, Zhang JH, Luo S, Hu JW, Sun K. The influence of physical activity, sedentary behavior on health-related quality of life among the general population of children and adolescents: A systematic review. PloS one. 2017; 12(11):e0187668-e.

5. Verswijveren SJ, Lamb KE, Bell LA, Timperio A, Salmon J, Ridgers ND. Associations between activity patterns and cardio-metabolic risk factors in children and adolescents: A systematic review. PloS one. 2018; 13(8):e0201947.

6. Fröberg A, Raustorp A. Objectively measured sedentary behaviour and cardio-metabolic risk in youth: a review of evidence. Eur J Pediatr. 2014; 173(7):845-60.

7. Cliff DP, Hesketh KD, Vella SA, Hinkley T, Tsiros MD, Ridgers ND, et al. Objectively measured sedentary behaviour and health and development in children and adolescents: systematic review and meta-analysis. Obes Rev. 2016; 17(4):330-44.

8. Hamilton MT, Hamilton DG, Zderic TW. Exercise physiology versus inactivity physiology: an essential concept for understanding lipoprotein lipase regulation. Exerc Sport Sci Rev. 2004; 32(4):161-6.

9. Hamilton MT, Hamilton DG, Zderic TW. Role of low energy expenditure and sitting in obesity, metabolic syndrome, type 2 diabetes, and cardiovascular disease. Diabetes. 2007; 56(11):2655-67.

10. Healy GN, Wijndaele K, Dunstan DW, Shaw JE, Salmon J, Zimmet PZ, et al. Objectively measured sedentary time, physical activity, and metabolic risk: The Australian Diabetes, Obesity and Lifestyle Study (AusDiab). Diabetes Care. 2008; 31(2):369-71.

11. Miles-Chan JL, Dulloo AG. Posture allocation revisited: breaking the sedentary threshold of energy expenditure for obesity management. Front Physiol. 2017; 8:420.

12. Biddle SJH, Pearson N, Salmon J. Sedentary Behaviors and adiposity in young people: causality and conceptual model. Exerc Sport Sci Rev. 2018; 46(1):18-25.

13. Fletcher EA, Carson V, McNaughton SA, Dunstan DW, Healy GN, Salmon J. Does diet mediate associations of volume and bouts of sedentary time with cardiometabolic health indicators in adolescents? Obesity (Silver Spring, Md). 2017; 25(3):591-9.

14. Ramos DE, Bueno MRO, Vignadelli LZ, Werneck AO, Ronque ERV, Coelho-E-Silva MJ, et al. Pattern of sedentary behavior in brazilian adolescents. Rev Bras Ativ Fis Saude. 2018; 23:1-6.

15. Júdice PB, Silva AM, Berria J, Petroski EL, Ekelund U, Sardinha LB. Sedentary patterns, physical activity and health-related physical fitness in youth: a cross-sectional study. Int J Behav Nutr Phy. 2017; 14(1):25.

16. Mendonça G, Prazeres Filho A, Barbosa AO, Farias Júnior JC. Padrões de comportamento sedentário em adolescentes de um município da região Nordeste do Brasil. Rev Bras Ativ Fis Saude. 2018; 23:1-9.

17. Tremblay MS, LeBlanc AG, Kho ME, Saunders TJ, Larouche R, Colley RC, et al. Systematic review of sedentary behaviour and health indicators in school-aged children and youth. Int J Behav Nutr Phys Act. 2011; 8:98.

18. Healy GN, Dunstan DW, Salmon J, Cerin E, Shaw JE, Zimmet PZ, et al. Breaks in sedentary time. Diabetes Care. 2008; 31(4):661.

19. Hamilton MT, Healy GN, Dunstan DW, Zderic TW, Owen N. Too little exercise and too much sitting: Inactivity physiology and the need for new recommendations on sedentary behavior. Curr Cardiovasc Risk Rep. 2008; 2(4):292.

20. Wilson AN, Olds T, Lushington K, Petkov J, Dollman J. The impact of 10-minute activity breaks outside the classroom on male students' on-task behaviour and sustained attention: a randomised crossover design. Acta Paediatr. 2016; 105(4):e181-8.

21. Chastin SF, Egerton T, Leask C, Stamatakis E. Meta-analysis of the relationship between breaks in sedentary behavior and cardiometabolic health. Obesity. 2015; 23(9):1800-10.

22. Poitras VJ, Gray CE, Borghese MM, Carson V, Chaput J-P, Janssen I, et al. Systematic review of the relationships between objectively measured physical activity and health indicators in school-aged children and youth. Appl Physiol Nutr Me. 2016; 41(6 (Suppl. 3)):S197-S239.

23. Carson V, Wong SL, Winkler E, Healy GN, Colley RC, Tremblay MS. Patterns of sedentary time and cardiometabolic risk among Canadian adults. Prev Med. 2014; 65:23-7.

24. Biddle SJH, Garcia Bengoechea E, Pedisic Z, Bennie J, Vergeer I, Wiesner G. Screen Time, Other Sedentary Behaviours, and Obesity Risk in Adults: A Review of Reviews. Curr Obes Rep. 2017; 6(2):134-47.

25. Carson V, Stone M, Faulkner G. Patterns of sedentary behavior and weight status among children. Pediatr Exerc Sci. 2014; 26(1):95-102.

26. Saunders TJ, Tremblay MS, Mathieu M-È, Henderson M, O'Loughlin J, Tremblay A, et al. Associations of sedentary behavior, sedentary bouts and breaks in sedentary time with cardiometabolic risk in children with a family history of obesity. PLoS ONE. 2013; 8(11):e79143.

27. Broadney MM, Belcher BR, Berrigan DA, Brychta RJ, Tigner IL, Shareef F, et al. Effects of interrupting sedentary behavior with short bouts of moderate physical activity on glucose tolerance in children with overweight and obesity: A randomized crossover trial. Diabetes Care. 2018; 41(10):2220-8.

28. Colley RC, Garriguet D, Janssen I, Wong SL, Saunders TJ, Carson V, et al. The association between accelerometer-measured patterns of sedentary time and health risk in children and youth: results from the Canadian Health Measures Survey. BMC Public Health. 2013; 13(1):200.

29. Kelly AS, Barlow SE, Rao G, Inge TH, Hayman LL, Steinberger J, et al. Severe obesity in children and adolescents: identification, associated health risks, and treatment approaches: a scientific statement from the American Heart Association. Circulation. 2013; 128(15):1689-712.

30. Umer A, Kelley GA, Cottrell LE, Giacobbi P, Jr., Innes KE, Lilly CL. Childhood obesity and adult cardiovascular disease risk factors: a systematic review with meta-analysis. BMC Public Health. 2017; 17(1):683.

31. Brasil. Ministério do Planejamento Orçamento e Gestão. Pesquisa Nacional por Amostra de Domicílios (PNAD) 2011. Rio de Janeiro: Instituto Brasileiro de Geografia e Estatística (IBGE). 2012.

32. Pinheiro ABV, Lacerda EMA, Benzecry EH, Gomes MCS, Costa VM. Tabela para avaliação de consumo alimentar em medidas caseiras. 5ª ed. São Paulo: Atheneu, 2008.

33. Verly-Jr E, Castro MA, Fisberg RM, Marchioni DML. Precision of usual food intake estimates according to the percentage of individuals with a second dietary measurement. J Acad Nutr Diet. 2012; 112(7):1015-20.

34. Trumbo P, Yates AA, Schlicker S, Poos M. Dietary reference intakes: vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. J Am Diet Asso. 2001; 101(3):294-301.

35. World Health Organization Multicentre Growth Reference Study Group. WHO child growth standards. Methods and development: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age. . Disponível em: http://www.who.int/childgrowth/standards/technical_report/en/index.html. Acessado em 21/09/2015.

36. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972; 18(6):499-502.

37. Christofaro DGD, Fernandes RA, Gerage AM, Alves MJ, Polito MD, Oliveira AR. Validation of the Omron HEM 742 blood pressure monitoring device in adolescents. Arq Bras Cardiol. 2009; 92(1):10-5.

38. Evenson KR, Catellier DJ, Gill K, Ondrak KS, McMurray RG. Calibration of two objective measures of physical activity for children. J Sports Sci. 2008; 26(14):1557-65.

39. Altenburg TM, Chinapaw MJ. Bouts and breaks in children's sedentary time: currently used operational definitions and recommendations for future research. Prev Med. 2015; 77:1-3.

40. Owen N, Sparling PB, Healy GN, Dunstan DW, Matthews CE. Sedentary behavior: emerging evidence for a new health risk. Mayo Clin Proc. 2010; 85(12):1138-41.

41. Brocklebank LA, Falconer CL, Page AS, Perry R, Cooper AR. Accelerometer-measured sedentary time and cardiometabolic biomarkers: a systematic review. Prev Med. 2015; 76:92-102.

42. Ryan DJ, Stebbings G, Onambele G. The emergence of sedentary behaviour physiology and its effects on the cardiometabolic profile in young and older adults. Age. 2015; 37(5):89.

43. Belcher BR, Berrigan D, Papachristopoulou A, Brady SM, Bernstein SB, Brychta RJ, et al. Effects of interrupting children's sedentary behaviors with activity on metabolic function: a randomized trial. J Clin Endocrinol Metab. 2015; 100(10):3735-43.

44. Butte NF, Watson KB, Ridley K, Zakeri IF, McMurray RG, Pfeiffer KA, et al. A youth compendium of physical activities: activity codes and metabolic intensities. Med Sci Sports Exerc. 2018; 50(2):246-56.

45. Pearson N, Braithwaite R, Biddle SJ, van Sluijs EM, Atkin AJ. Associations between sedentary behaviour and physical activity in children and adolescents: a meta-analysis. Obes Rev. 2014; 15(8):666-75.

46. Costa CS, Flores TR, Wendt A, Neves RG, Assunção MCF, Santos IS. Comportamento sedentário e consumo de alimentos ultraprocessados entre adolescentes brasileiros: Pesquisa Nacional de Saúde do Escolar (PeNSE), 2015. Cad Saude Publica. 2018; 34:e00021017.

47. Katon JG, Flores YN, Salmeron J. Sexual maturation and metabolic profile among adolescents and children of the Health Worker Cohort Study in Mexico. Salud Publica Mex. 2009; 51(3):219-26.

48. Mascarenhas LP, Leite N, Titski AC, Brito LM, Boguszewski MC. Variability of lipid and lipoprotein concentrations during puberty in Brazilian boys. J Pediatr Endocrinol Metab. 2015; 28(1-2):125-31.

49. Piola TS, Bacil EDA, Silva MP, Campos JG, Neto NAM, Campos W. Comportamento sedentário em adolescentes: análise hierárquica de fatores associados. Revista Contexto Saúde. 2019; 19(37):128-36.

50. Banda JA, Haydel KF, Davila T, Desai M, Bryson S, Haskell WL, et al. Effects of varying epoch lengths, wear time algorithms, and activity cut-points on estimates of child sedentary behavior and physical activity from accelerometer data. PLoS One. 2016; 11(3):e0150534.

51. Stålesen J, Vik FN, Hansen BH, Berntsen S. Comparison of three activity monitors for estimating sedentary time among children. BMC Sports Sci Med Rehabilitation. 2016; 8(1):2.

Is Adolescents' Cardiometabolic Health Affected by Prolonged Periods of Inactivity?

Andrea Wendt[1]

Universidade Federal de Pelotas (UFPEL),[1] *Pelotas, RS – Brazil*

Short Editorial related to the article: Breaks in Sedentary Time and Cardiometabolic Markers in Adolescents

The current literature regarding physical activity (PA) and sedentary behavior (SB) highlights the negative effect of considerable amounts of time spent in activities such as sitting, TV viewing, computer use, and some work and study activities on cardiovascular health.[1] SB may be defined as any waking behavior characterized by an energy expenditure ≤ 1.5 metabolic equivalents while in a sitting, reclining, or lying posture.[2,3] Thus, SB is not the absence or low level of PA, but it can coexist with it.[2] In this sense, a recent review showed an interaction between SB and PA, providing evidence that individuals with higher time spent in SB presented a higher risk of cardiovascular mortality. However, estimates have been less consistent in individuals with higher PA levels.[4]

The literature cites a series of possible mechanisms for SB effects, independent of PA, on metabolic and cardiovascular outcomes. One of these mechanisms is the decrease in enzymatic activity responsible for HDL production and the capture of triglycerides in the blood chain due to sustained inactivity in sitting, reclining, or lying posture.[1] In this regard, strategies reducing the time spent in SB or interrupting sustained inactivity have been studied. Some of these approaches focus on standing up for a while or a short period of movement between periods of sitting time (breaks in SB). A meta-analysis with adults found a positive effect of breaks in SB on adiposity control and glycemia.[5] In addition, an experimental study showed that 1-to-2–minute breaks in sedentary work activities every half an hour resulted in small-to-moderate declines in total cholesterol, triglycerides, and fasting blood glucose.[6]

Keywords

Cardiovascular Diseases/physiopathology; Metabolic Diseases; Motor Activity; Sedentarism; Adolescent, Cholesterol; Triglycerides; Body Mass Index; Epidemiology.

Mailing Address: Andrea Wendt •
Marechal Deodoro, 1160, 3º andar. Postal Code 96020-220, Centro, Pelotas, RS – Brazil
E-mail: andreatwendt@gmail.com

DOI: https://doi.org/10.36660/abc.20210479

While the literature about breaks was developed focusing mainly on adult populations and exploring interruptions in sedentary work activities, studies with children and adolescents are scarce, especially in low- and middle-income countries. Furthermore, the evaluation of the effects of breaks on adolescent health should be reinforced, given that cardiometabolic risks are already present at this age,[7-10] which is also marked by sustained sedentary school activities. Faced with this scenario, Quirino et al.,[11] in a study published in this volume, verified the association of breaks in SB on cardiometabolic risk in an adolescent sample. This cross-sectional study comprised data of 573 adolescents from João Pessoa, Paraíba, Brazil and objectively measured breaks in SB using accelerometers. Systolic and diastolic blood pressure, fasting glucose, total cholesterol, triglycerides, HDL, LDL, and body mass index (BMI) were the assessed outcomes.[11] The authors found that a higher number of breaks in SB decreased BMI by −0.102 kg/m. Statistically significant effects for other outcomes were not found. However, the direction of associations was towards more breaks reducing negative outcomes. The literature with adult samples has found associations with many outcomes, different from the results found in this paper. The authors bring, as one explanation for this finding, the differences in movement patterns for children/adolescents. Children and adolescents, in general, have a movement pattern with more peaks of high-intensity PA and short inactivity windows (sedentary time sustained for less time).[12,13]

The study raises some future research questions for the area: How long should breaks in SB be in order to obtain a positive effect on adolescent health? Do PA levels modulate breaks in SB for this population? Which is the ideal pattern of breaks supposed to improve cardiometabolic health (only standing up or a few minutes of light PA)? Answering these questions may help to plan school-based strategies for this population group. Last but not least, it is important to highlight that the current COVID-19 pandemic may have increased the time spent in SB by the general population,[14,15] including children and adolescents. Thus, interventions increasing the time spent in PA and breaks in SB, which should be encouraged in normal situations, are likely even more relevant in this alarming scenario.

References

1. Carter S, Hartman Y, Holder S, Thijssen DH, Hopkins ND. Comportamento sedentário and Cardiovascular Disease Risk: Mediating Mechanisms. Exercise and Sport Sciences Reviews. 2017;45(2):80-6.
2. Tremblay MS, Aubert S, Barnes JD, Saunders TJ, Carson V, Latimer-Cheung AE, et al. Sedentary Behavior Research Net Work (SBRN). Int J Beahv Nutr Phys Act. 2017;14(1):75.
3. Letter to the editor Sedentary Behaviours. Appl Physiol Nutr Metab. 2012;37(3):540-2.
4. Ekelund U, Brown WJ, Steene-Johannessen J, Fagerland MW, Owen N, Powell KE, et al. Do the associations of comportamento sedentário with cardiovascular disease mortality and cancer mortality differ by atividade física level? A systematic review and harmonised meta-analysis of data from 850 060 participants. British journal of sports medicine. 2019;53(14):886-94.
5. Chastin SF, Egerton T, Leask C, Stamatakis E. Meta-analysis of the relationship between breaks in comportamento sedentário and cardiometabolic health. Obesity (Silver Spring, Md). 2015;23(9):1800-10.
6. Mailey EL, Rosenkranz SK, Casey K, Swank A. Comparing the effects of two different break strategies on occupational comportamento sedentário in a real world setting: A randomized trial. Prev Med Rep. 2016 Aug 9;4:423-8.
7. Chacra APM. The Importance of Identifying Risk Factors in Childhood and Adolescence. Arq Bras Cardiol. 2019;112(2):152-3.
8. Tozo TA, Pereira BO, Menezes Junior FJ, Montenegro CM, Moreira CMM, Leite N. Hypertensive measures In schoolchildren risk of central obesity and protective effect of moderate-to-vigorous. Arq Bras Cardiol. 2020;115(1):42-9.
9. Jesus GDS, Costa PRF, Oliveira LPM, Queiroz VAO, Cunha CM, Pereira EM, et al. Body adiposity and apolipoproteins in children and adolescents: a meta-analysis of prospective studies. Arq Bras Cardiol. 2020;115(2):163-71.
10. Reuter CP, Brand C, Silva PTD, Reuter É M, Renner JDP, Franke SIR, et al. Relationship between dyslipidemia, cultural factors, and cardiorespiratory fitness in schoolchildren. Arq Bras Cardiol. 2019;112(6):729-36.
11. Quirino N, Prazeres Filho A, Borbosa A, Mendonça G, Farias Jr J. Breaks in sedentary time and cardiometabolic markers in adolescents. Arq Bras Cardiol. 2021; 117(2):352-362. doi: https://doi.org/10.36660/abc.20200047
12. Wang WY, Hsieh YL, Hsueh MC, Liu Y, Liao Y. Accelerometer-measured Patterns in Taiwanese adolescents. Int J Environ Res Publ Health. 2019;16(22):439-42.
13. van Ekris E, Wijndaele K, Altenburg TM, Atkin AJ, Twisk J, Andersen LB, et al. Tracking of total sedentary time and sedentary patterns in youth: a pooled analysis using the International Children's Accelerometry Database (ICAD). Int J Behav Nutr Phys Act. 2020;17(1):65.
14. Botero JP, Farah BQ, Correia MA, Lofrano-Prado MC, Cucato GG, Shumate G, et al. Impact of the COVID-19 pandemic stay at home order and social isolation on atividade física levels and comportamento sedentário in Brazilian adults. Einstein (Sao Paulo, Brazil). 2021;19:eAE6156.
15. Silva D, Werneck AO, Malta DC, Souza Júnior PRB, Azevedo LO, Barros MBA, et al. Changes in the prevalence of inatividade física and comportamento sedentário during COVID-19 pandemic: a survey with 39,693 Brazilian adults. Cad Saude Publ. 2021;37(3):e00221920.

The Effect of Atorvastatin + Aspirin on the Endothelial Function Differs with Age in Patients with HIV: A Case-Control Study

Gerson Gomes dos Santos Junior,[1,2] Paulo Sérgio Ramos Araújo,[1,3] Kaliene Maria Estevão Leite,[1] Emmanuelle Tenório Godoi,[4] Adriana Ferraz Vasconcelos,[4] Heloisa Ramos Lacerda[1,4]

Universidade Federal de Pernambuco - Pós-graduação em Medicina Tropical,[1] Recife, PE - Brazil

Universidade Federal de Alagoas - Instituto de Ciências Farmacêuticas,[2] Maceió, AL - Brazil

Instituto de Pesquisa Aggeu Magalhães,[3] Recife, PE - Brazil

Universidade Federal de Pernambuco - Medicina Clínica,[4] Recife, PE - Brazil

Abstract

Background: **Patients with HIV are more likely to present with cardiovascular disease when compared to the general population.**

Objective: **This was a case-control study that aimed to assess which factors were associated with a reduction in the carotid intima-media thickness (IMT) and an increase in the brachial artery flow-mediated dilation (FMD) in HIV patients who received atorvastatin + aspirin during a period of 6 months.**

Methods: **A secondary analysis of a clinical trial was conducted, which included people living with HIV infection and low cardiovascular risk. A total of 38 patients allocated to the intervention arm and treated for 6 months with a combination of atorvastatin + aspirin were included. All participants underwent a carotid and brachial artery ultrasound, both at the beginning and the end of the study. Cases that responded with an increase of >10% of the brachial dilatation (FMD) and reduction of the carotid intima-media thickness (IMT) were considered cases, and those who did not respond were considered controls. We assessed the factors associated with the positive responses obtained through IMT and FMD.**

Results: **A reduction in the IMT was not significantly associated with any of the evaluated risk factors: age (p=0.211), gender (p=0.260), smoking (p=0.131) or time since HIV diagnosis (p=0.836). An increase in the FMD was significantly associated with age amongst those in the 40-59 age group, p = 0.015 (OR = 4.37; 95% CI: 1.07-17.79).**

Conclusions: **Older individuals were more likely to present with an increased FMD after 6 months of treatment with atorvastatin + aspirin.**

Keywords: **HIV; Carotid Arteries/ultrasonography; Carotid Intima-Media Thickness;Brachial Artery; Atorvastatin; Aspirin; Risk Factors; Endothelium Vascular/physiopathology; Atorvastatin; Aspirin;Risk Factors; Endothelium Vascular/physiopathology.**

Introduction

Life expectation and quality of life among people infected with HIV has increased significantly over recent decades. This is due to the great success of antiretroviral therapy.[1] Living with the virus has now become a chronic condition, which imposes the challenge of maintaining viral suppression coupled with the management of age-related comorbidities.[2] A substantial increase in non-AIDS-related deaths, such as those related to cardiovascular diseases, has been reported,[3] and are more prevalent in these individuals, when compared to the general population.[4,5]

An early marker for atherosclerosis is endothelial dysfunction and preventing this dysfunction may be an alternative for preventing future cardiovascular events. Aspirin and, more recently, statins have demonstrated pleiotropic effects, such as: immunomodulatory, and antithrombogenic and anti-inflammatory effects. Such medications may be an alternative for the primary and secondary prevention of these events among people living with HIV.[6-8]

Observational and interventional studies have evaluated the effects of statins in improving endothelial function, and the progression of carotid thickening in individuals both with and without HIV. These studies have used non-invasive ultrasound techniques, such as FMD, which measures the mediated flow of the brachial artery, and IMT, which measures carotid intima-media thickening, and have reported conflicting results.[9-12] To contribute to this discussion, our study aims to assess the factors associated with endothelial function improvement and carotid thickness measured by FMD and IMT in subjects with HIV, with a viral load under control, who were treated with a combination of atorvastatin + aspirin for a period of 6 months.

Mailing Address: Gerson Gomes dos Santos Junior •
Universidade Federal de Pernambuco - Pós-graduação em Medicina Tropical - Av. Prof. Moraes Rego, 1235. Postal Code 50670-901, Cidade Universitária, Recife, PE – Brazil
E-mail: gergomes@yahoo.com.br
Manuscript received January 26, 2020, revised manuscript August 14, 2020, accepted August 16, 2020

DOI: https://doi.org/10.36660/abc.20190844

Methods

This was a secondary analysis of a clinical trial not yet published[13] in which 80 participants who presented with low cardiovascular risk, as measured by the Framingham Risk Score (FRS), and an undetectable viral load were assessed.

The study was planned for 6 months, using 2 nucleoside reverse transcriptase inhibitors and 1 non-nucleoside inhibitor regimens, which were randomized into intervention and placebo groups. Thirty-eight participants were allocated to the intervention group and treated for 6 months with a combination of 20mg atorvastatin + 100mg aspirin, and 42 received placebo. The study assessed the efficacy of the drug combination through ultrasound measurements of the increased brachial artery dilation (FMD), reduced carotid thickening (IMT), and inflammatory markers (ultrasensitive-PCR, ICAM-1, VCAM-1, IL-1, IL-6, TNF-α) and no difference was found between the intervention group and the placebo group.

In the case-control study presented herein, 38 individuals from the intervention group of the aforementioned clinical trial were included. The aim was to assess subgroups that could benefit from the use of atorvastatin 20mg and aspirin 100mg in reducing subclinical atherosclerosis and cardiovascular disease.

In the first part of the case-control study, a total of 38 individuals were divided into 24 cases, which were those who had a favorable response in FMD (≥10% of brachial artery dilation according to the method described by Regattieri et al.[14] and 14 patients who were considered controls, as they did not show response in FMD.

In the second part of the case-control study, the 38 subjects were divided into 29 cases, which were the individuals who showed a reduction in the carotid IMT, and 9 controls who did not show a reduction in the carotid IMT.

All individuals signed the free and informed consent form. The study was approved by the Research Ethics Committee of Universidade Federal de Pernambuco, under number 13097213.2.0000.5208. The clinical trial was registered at the International Clinical Trials Registry Platform (RBR-bjm4) and conducted at the Infectious/Parasitic Diseases Outpatient Clinic at Hospital das Clínicas, Universidade Federal de Pernambuco/Recife, Brazil.

Vascular measurements

A General Electric™ (GE) LOGIQe BT12 DICOM 3.0 AUTO IMT ultrasound device was used, with a GE 9-L RS Linear transducer, working at a frequency of 7-10 MHz. The measurements were performed according to standardized techniques.[15,16]

FMD: The brachial artery diameter was measured at rest and after stimulation. To stimulate the brachial artery, a Becton Dickinson™ sphygmomanometer placed on the arm was inflated to 30mmHg above the systolic pressure for 5 minutes, and then released. One minute after releasing the clamp, the diameter of the artery was measured once again. Normal dilation was considered > 10% - Figures 1 and 2.

IMT: The common carotid intima-media thickness in a plaque-free area was considered a reference measure. It was assessed in the longitudinal and cross-sectional sections, from the proximal segment to the bifurcation and the internal and external carotids. The IMT was measured on the posterior wall of the common carotid in a plaque-free area. The carotid plaque was defined as a focal structure extending for a minimum of 0.5 mm to the lumen of the vessel and/or measuring more than 50% of the adjacent IMT value and/or an IMT measurement greater than 1.5 mm[17] (Figure 3).

Statistical analysis

The data were descriptively analyzed through the statistics: mean, standard deviation (mean ± SD) or median and interquartile range (IQR) for numerical variables and absolute and percentage frequencies for categorical variables and were analyzed inferentially through statistical tests. In the comparison between two categories, the following tests were used: unpaired Student's t-test with equal variances or Mann-Whitney test for the numerical variables and Pearson's Chi-square test or Fisher's Exact for the categorical variables. Student's t-test was used with variables with normal distribution and Mann-Whitney's test with variables with a non-normal distribution. Fisher's Exact test was used in cases where the condition for using the Chi-square test was not verified. The verification of data normality was performed by the Shapiro-Wilk's test and the hypothesis of equality of variances through the Levene F-test. The level of statistical significance adopted was 5% and the confidence intervals were 95.0%

The data were entered into the EXCEL spreadsheet and the IMB-SPSS program, version 23, was used to perform the statistical calculations.

Results

The characteristics of the 38 subjects included in the study are described in Table 1. The results demonstrated: mean age (42.6 years), time since diagnosis (median – 6.5 years), antiretroviral therapy time (median - 6.0 years). Characteristics of the sample: male gender (52.6%), hypertensive (7.9%), diabetics (5.3%), smokers (15.8%). Some characteristics were described by subgroup, such as age (21-39 and 40-59 years), ethnicity (white, black and brown), and nutritional status (ideal weight, overweight and obesity).

Factors associated with brachial artery flow-mediated dilation (FMD)

A statistically significant difference was obtained for the mean age ($p = 0.015$). When age ranges were assessed (21-39 years and 40-59 years), the significance was maintained ($p = 0.034$). When assessing the older age group, it was observed that there was an excellent response to brachial artery dilation (OR=4.37, CI 95%: 1.07 - 17.79), compared to that obtained in the 21- 39 year-old group.

When we assessed the outcome regarding sex, a borderline result was obtained ($p = 0.076$, with an OR = 3.5 (CI 95%: 0.85-14.41) for female subjects. The other risk factors assessed did not show any statistical significance: systemic arterial

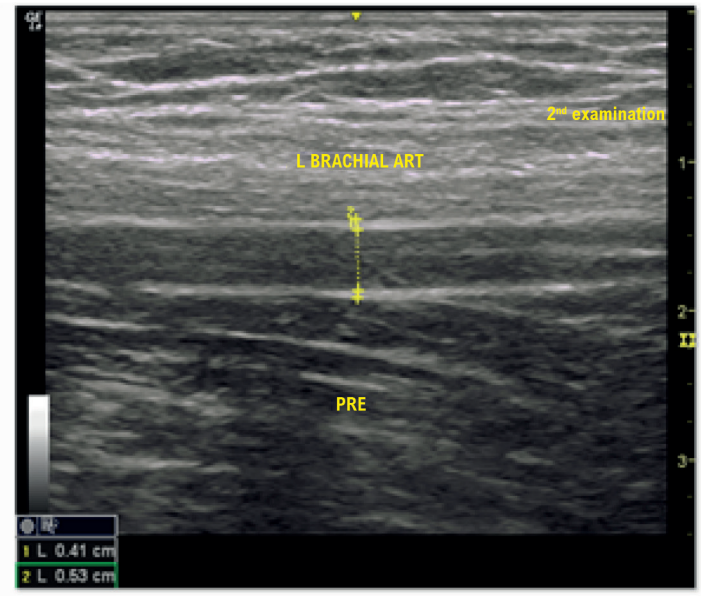


Figure 1 - *Measurement of the left brachial artery before the stimulus.*

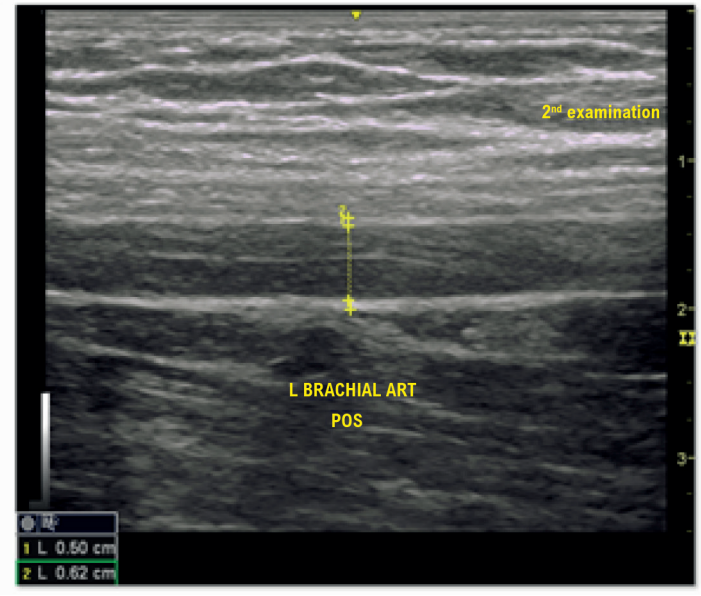


Figure 2 - *Medida da artéria braquial esquerda após o estímulo.*

hypertension (SAH, p = 0.542); diabetes mellitus (DM; p = 1.00); smoking (p = 0.383) in Table 2.

Factors associated with a reduction in the carotid intima-media thickness (IMT)

No statistically significant differences were observed for any of the variables assessed in relation to a reduction in the carotid intima-media thickness: age (p = 0.706); gender (p = 0.260), SAH and DM (p = 1.00); smoking (p = 0.131), BMI (p = 0.945), as shown in Table 3.

Discussion

Our study assessed patients living with HIV, receiving antiretroviral therapy and with a low cardiovascular risk, who

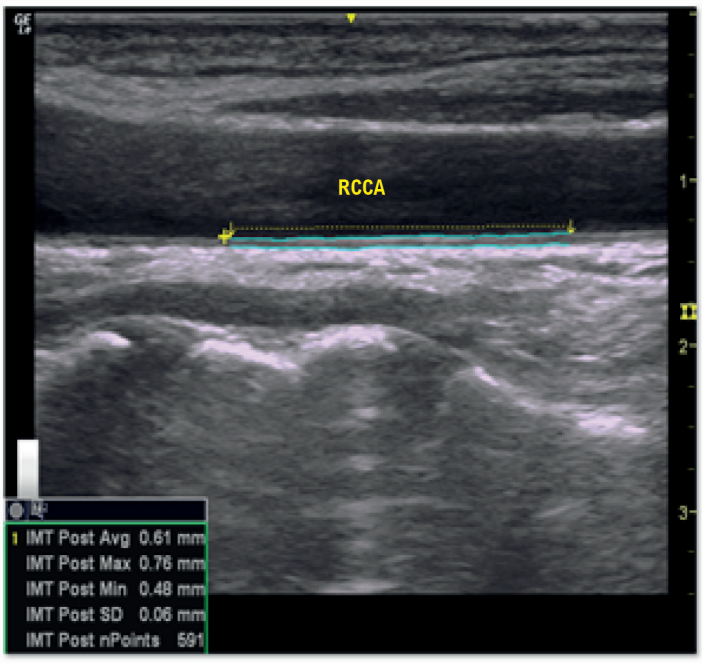


Figure 3 – *Mean intimal thickness measurement of the right carotid artery.*

took a combination of atorvastatin + aspirin during a period of 6 months. An exploratory analysis was performed in order to evaluate the factors associated with a positive response to the treatment assessed through FMD and IMT vascular techniques.

The results have demonstrated that individuals belonging to the older age group (between 40 and 59 years) responded positively to a combination of atorvastatin + aspirin, i.e., with increased FMD by the end of the study. It may be inferred that older individuals have been exposed for a longer period to the inflammation resulting from the HIV. It is known that there are higher levels of inflammation in people with HIV than in non-infected people, even those under virological control, and this exposure is an important factor in the genesis of endothelial dysfunction. These findings are similar to those obtained by other authors, who have verified that a high level of virus replication results in a brachial artery dilation worsening.[18] Conversely, the higher the viral control, the better the endothelial function.[19] Another hypothesis would be that individuals at an older age range would be more prone to the consequences of the age-related atherosclerotic process and more sensitive to the deleterious effects of HIV on the endothelium. In turn, our findings may suggest that these older individuals would be more responsive to the pleiotropic and anti-inflammatory actions of the combination of atorvastatin + aspirin. Our findings suggest that there is a benefit of the use of statins + aspirin as a primary prophylaxis for cardiovascular disease in individuals with HIV, which should be assessed differently in individuals according to their age group, particularly individuals aged 40 years or older.[20,21]

When we assessed the response related to gender, we obtained a borderline result, in which the OR for the female group was equal to 3.5. Although there was no statistical significance, this response nonetheless attracted our attention, since it suggests that females may respond better to treatment with atorvastatin + aspirin than males. Studies have suggested that amongst people living with HIV, women show higher levels of immune activation and inflammation than men.[22] Considering that the currently used medications have an important effect in reducing inflammation, a mechanism intrinsically related to the progression of atherosclerosis, one could infer that this may be the possible reason for a more evident response in women than in men. Our study, however, was unable to confirm this association, but others that have assessed a larger number of individuals may have sufficient power to obtain statistical significance. Studies that associate gender with response to endothelial function would be necessary.

The antiretroviral regimens used were not significantly associated with FMD and IMT responses; however, they only included analogue and non-analogue nucleoside NRTIs. Patients receiving protease inhibitors (PIs) or integrase inhibitors (INI) were not included. It is known that amongst the currently used medications, the PIs cause more metabolic disorders than the others and, consequently, they predispose to a higher cardiovascular risk.[23] Dube et al.,[24] in a cross-sectional study comparing individuals with or without the use of PIs, observed no difference regarding the response to FMD. However, several other authors have discovered greater carotid thickening measured by IMT in those receiving PIs when compared to those not receiving them.[25,26]

The use of regimens with restricted groups of antiretroviral drugs have aimed to homogenize the comparison groups and

Table 1 – Clinical and demographic characteristics of the 38 study participants

Variable	TOTAL
Total Group:	**38 (100,0)**
Age: Mean ± SD (Median)	42.6 ± 8.8 (43.0)
Age range: n (%)	
21 to 39	16 (42)
40 to 59	22 (58)
Gender: n (%)	
Male	20 (52.6)
Female	18 (47.4)
Ethnicity: n (%)	
White	15 (39.5)
Black	4 (10.5)
Brown	19 (50)
Level of education: n (%)	
Primary Education	13 (34.2)
Secondary Education	18 (47.3)
Higher Education	7 (18.4)
BMI: Median (P25;IR;P75)	24.2 (21.6; 6.6; 28.2)
Nutritional status: n (%)	
Ideal weight	23 (60.5)
Overweight	8 (21.0)
Obese	7 (18.4)
SBP: Median (P25;IR;P75)	120.00 (110.0; 10.0; 120.0)
DBP: Median (P25;IR;P75)	80.00 (70.0; 10.0; 80.0)
SAH: n (%)	
Yes	3 (7.9)
No	35 (92.1)
Family history of cardiovascular disease: n (%)	
Yes	12 (31.6)
No	26 (68.4)
DM: n (%)	
Yes	2 (5.3)
No	36 (94.7)
Smoker: n (%)	
Yes	6 (15.8)
No	32 (84.2)
Time since diagnosis: Median (P25;IQR;P75)	6.50 (4.0; 8.0; 12.0)
Time since diagnosis: n (%)	
Up to 1 year	4 (10.5)
2 to 5	12 (31.6)
6 to 10	12 (31.6)
Over 10	10 (26.3)
Time on ART: Median (P25;IQR;P75)	6.00 (2.0; 7.8; 9.8)
Up to 1 year: n (%)	5 (13.2)
2 to 5	13 (34.2)
6 to 10	11 (28.9)
Over 10	9 (23.7)
NadirTCD4: Mean ± SD (Median)	362.3 ± 239.5 (340.5)
CD4: Mean ± SD (Median)	724.0 ± 354.7 (659.5)
Regimen: n (%)	
AZT+ 3 TC + EFV	21 (55.3)
TDF + 3TC + EFV	13 (34.2)
AZT + 3TC + NEV	1 (2.6)
NEV + 3TC + TDF	2 (5.26)
AZT + DDI + EFV	1 (2.6)

Data are presented as means, standard deviation (SD), medians, Interquartile Range (IQR), percentile (P) or n (%) of individuals. BMI: body mass index; DM: diabetes mellitus; SBP: systolic blood pressure; DBP: diastolic blood pressure; SAH: systemic arterial hypertension; ART: antiretroviral therapy; AZT: zidovudine; DDI: didanosine; EFV: efavirenz; 3-TC: lamivudine; NVP: nevirapine; TDF: tenofovir.

prevent medications from becoming confounding factors regarding the response to atorvastatin + aspirin.

Smoking was not associated with FMD or IMT responses. It should be emphasized that the low prevalence of smoking may have made it difficult to assess the role it played. However, it should be noted that in the IMT assessment, non-smokers showed a 4.3-fold higher chance of obtaining an IMT reduction with atorvastatin + aspirin. However, probably due to the small number of cases, the confidence interval was high (0.70 - 27.01) and there was no statistical significance. One recent study demonstrated that smoking results in poor viral control and immune response,[27] which, as previously mentioned, results in a higher cardiovascular risk. One cohort study related smoking to a worsening progression of carotid thickening.[28] Studies with a higher number of patients are necessary in order to determine the role of this intervention in smokers.

Our findings revealed no association between obesity and an endothelial function response measured by FMD, or carotid thickness (IMT) progression after receiving atorvastatin + aspirin. A cohort study that monitored obese patients with HIV and compared them with non-HIV-infected obese individuals, demonstrated a higher incidence of glucose metabolism disorders and inflammation amongst those with HIV, although FMD and IMT did not differ between the two groups.[29] Data have reported a relationship between lipodystrophy and poor endothelial function[30] and increased carotid thickening, especially among individuals with visceral obesity.[31] In our study, we did not diagnose lipodystrophy. We only assessed body composition with the body mass index (BMI) and classified individuals according to low weight, normal weight, overweight or obesity. However, because there is a high prevalence of lipodystrophy among HIV patients, and BMI is not an index that may provide us

Table 2 – Factors associated with a favorable response to FMD amongst 38 patients receiving atorvastatin + aspirin, with low cardiovascular risk and an undetectable viral load

	FMD			
Variable	**Favorable response (Cases)**	**No response (Controls)**	**p-value**	**OR (95%CI)**
Total Group:	24 (63.2)	14 (36.8)		
Age: Mean ± SD (Median)	45.3 ± 8.8 (46.0)	38.1 ± 7.2 (36,5)	p(3) = 0.015*	
Age Range: n (%)			p(2) = 0.034*	
21 to 39	7 (43.8)	9 (56.3)		1.00
40 to 59	17 (77.3)	5 (22.7)		4.37 (1.07-17.79)
Gender: n (%)			p(2) = 0.076	
Male	10 (50.0)	10 (50.0)		1.00
Female	14 (77.8)	4 (22.2)		3.50 (0.85-14.41)
Ethnicity: n (%)			p(2) = 0.744	
White	9 (60.0)	6 (40.0)		1.00
Non-white	15 (65.2)	8 (34.8)		1.25 (0.33-4.79)
Level of education: n (%)			p(4) = 0.157	
Primary Education	11 (84.6)	2 (15.4)		**
Secondary Education	9 (50.0)	9 (50.0)		**
Higher Education	4 (57.1)	3 (42.9)		**
BMI: Mean ± SD (Median)	24.6 ± 4.9 (23,1)	26.5 ± 4.6 (24,9)	p(3) = 0.250	
Nutritional status: n (%)			p(4) = 0.574	
Ideal weight	16 (69.6)	7 (30.4)		1.71 (0.30-9.77)
Overweight	4 (50.0)	4 (50.0)		0.75 (0.10-5.77)
Obese	4 (57.1)	3 (42.9)		1.00
SBP: Median (P25;IQR;P75)	120,0 (110,0;17,5; 127,5)	120,0(110,0;10,0;120,0)	p(1) = 0.747	
DBP: Median (P25;IQR;P75)	80,00 (70,0; 10,0; 80,0)	80,00 (70,0; 12,5; 82,5)	p(1) = 0.767	
SAH: n (%)			p(4) = 0.542	
Yes	1 (33.3)	2 (66.7)		**
No	23 (65.7)	12 (34.3)		
Family history of cardiovascular disease: n (%)			p(4) = 1.000	
Yes	8 (66.7)	4 (33.3)		1.25 (0.30-5.26)
No	16 (61.5)	10 (38.5)		1.00
DM: n (%)			p(4) = 1.000	
Yes	1 (50.0)	1 (50.0)		**
No	23 (63.9)	13 (36.1)		
Smoker: n (%)			p(4) = 0.383	
Yes	5 (83.3)	1 (16.7)		**
No	19 (59.4)	13 (40.6)		
Time since diagnosis: Mean ± SD (Median)	8.3 ± 4.8 (8.0)	6.4 ± 5.3 (4.0)	p(3) = 0.264	
Time since diagnosis: n (%)			p(2) = 0.152	
Up to 5 years	8 (50.0)	8 (50.0)		1.00
6 or more years	16 (72.7)	6 (27.3)		2.67 (0.69-10.36)
Time on ART: Median (P25;IQR;P75)	6.50 (3.0; 8.3; 11.3)	3.50 (1.8; 7.2; 9.0)	p(1) = 0.149	

Continuation

Time on ART: n (%)			$p^{(2)}$ = 0.111	
Up to 5 years	9 (50.0)	9 (50.0)		1.00
6 or more years	15 (75.0)	5 (25.0)		3.00 (0.76-11.81)
NadirTCD4: Mean ± SD (Median)	373.8 ± 247.8 (332,5)	342.6 ± 232.3 (354.0)	$p^{(3)}$ = 0.704	
CD4: Mean ± SD (Median)	754.3 ± 391.5 (659.5)	672.1 ± 286.8 (677.5)	$p^{(3)}$ = 0.499	
Regimen: n (%)			$p^{(4)}$ = 0.724	
AZT + 3TC + EFV	13 (61.9)	8 (38.1)		**
TDF + 3TC + EFV	9 (69.2)	4 (30.8)		**
AZT + 3TC + NEV	-	1 (100.0)		**
NEV + 3TC + TDF	1 (50.0)	1 (50.0)		**
AZT + DDI + EFV	1 (100.0)	-		**

Data are presented as means, standard deviation (SD), medians, Interquartile Range (IQR), percentile (P) or n (%) of individuals. (*) Significant difference at the level of 5.0%. (**) This could not be determined due to the occurrence of null and very low frequencies. (1) Using Mann-Whitney test. (2) Using Pearson's Chi-square test. (3) Using the Student's t test with equal variances. (4) Using Fisher's exact test. BMI: body mass index; DM: diabetes mellitus; SBP: systolic blood pressure; DBP: diastolic blood pressure; SAH: systemic arterial hypertension; ART: antiretroviral therapy; AZT: zidovudine; DDI, didanosine; EFV, efavirenz; 3-TC, lamivudine; NVP, nevirapine; TDF, tenofovir.

Table 3 – Factors associated with a reduction in carotid IMT amongst 38 patients receiving atorvastatin + aspirin, with low cardiovascular risk and an undetectable viral load

	IMT			
Variable	**Reduction (Cases)**	**No reduction (Controls)**	**p-value**	**OR (95% CI))**
Total Group:	29 (76.3)	9 (23.7)		
Age: Mean ± SD (Median)	41.6 ± 8.9 (43.0)	45.9 ± 8.0 (46.0)	$p^{(1)}$ = 0.211	
Age range: n (%)			$p^{(2)}$ = 0.706	
21 to 39	13 (81.3)	3 (18.8)		1.63 (0.34-7.79)
40 to 59	16 (72.7)	6 (27.3)		1.00
Gender: n (%)			$p^{(2)}$ = 0.260	
Male	17 (85.0)	3 (15.0)		2.83 (0.59-13.63)
Female	12 (66.7)	6 (33.3)		1.00
Ethnicity: n (%)			$p^{(2)}$ = 1.000	
White	11 (73.3)	4 (26.7)		1.00
Non-white	18 (78.3)	5 (21.7)	.	1.31 (0.29-5.95)
Level of education: n (%)			$p^{(2)}$ = 0.782	
Primary Education	9 (69.2)	4 (30.8)		**
Secondary Education	14 (77.8)	4 (22.2)		**
Higher Education	6 (85.7)	1 (14.3)		**
BMI: Median (P25;IQR;P75)	24.20 (21.7; 5.9; 27.6)	23.18 (21.4; 9.3; 30.7)	$p^{(3)}$ = 0.945	
Nutritional status:			$p^{(2)}$ = 0.757	
Ideal weight	17 (73.9)	6 (26.1)		**
Overweight	7 (87.5)	1 (12.5)		**
Obese	5 (71.4)	2 (28.6)		**
SBP: Median (P25;IQR;P75)	120.00 (110.0;10.0; 120.0)	120.00 (110.0; 30.0; 140.0)	$p^{(3)}$ = 0.272	
DBP: Median (P25;IQR;P75)	80.00 (70.0; 10.0; 80.0)	80.00 (70.0; 15.0; 85.0)	$p^{(3)}$ = 0.653	

Continuation

SAH: n (%)			$p^{(2)}$ = 1.000	
Yes	3 (100.0)	-		**
No	26 (74.3)	9 (25.7)		
Family history of cardiovascular disease: n (%)			$p^{(2)}$ = 0.423	
Yes	8 (66.7)	4 (33.3)		1.00
No	21 (80.8)	5 (19.2)		2.10 (0.45-9.86)
DM: n (%)			$p^{(2)}$ = 1.000	
Yes	2 (100.0)	-		**
No	27 (75.0)	9 (25.0)		
Smoker: n (%)			$p^{(2)}$ = 0.131	
Yes	3 (50.0)	3 (50.0)		1.00
No	26 (81.3)	6 (18.8)		4.33 (0.70- 27.01)
Time since diagnosis: Median (P25;IQR;P75)	6.00 (4.0; 8.0; 12.0)	8.00 (3.5; 7.5; 11.0)	$p^{(3)}$ = 0.836	
Time since diagnosis: n (%)			$p^{(2)}$ = 0.706	
Up to 5 years	13 (81.3)	3 (18.7)		1.63 (0.34-7.79)
6 or more years	16 (72.7)	6 (27.3)		1.00
Time on ART: Median (P25;IQR;P75)	6.00 (2.5; 9.5; 12.0)	6.00 (2.0; 6.5; 8.5)	$p^{(3)}$ = 0.593	
Time on ART: n (%)			$p^{(2)}$ = 1.000	
Up to 5 years	14 (77.8)	4 (22.2)		1.17 (0.26-5.24)
6 or more years	15 (75.0)	5 (25.0)		1.00
NadirTCD4: Mean ± SD (Median)	350.2 ± 236.9 (315.0)	401.3 ± 258.2 (401.0)	$p^{(1)}$ = 0.583	
CD4: Mean ± SD (Median)	750.8 ± 375.6 (677.0)	637.5 ± 277.7 (574.0)	$p^{(1)}$ = 0.410	
Regimen: n (%)			$p^{(2)}$ = 1.000	
AZT+3TC + EFV	15 (71.4)	6 (28.6)		**
TDF + 3TC + EFV	10 (76.9)	3 (23.1)		**
AZT+3TC + NEV	1 (100.0)	-		**
NEV + 3TC + TDF	2 (100.0)	-		**
AZT + DDI + EFV	1 (100.0)	-		**

Data are presented as means, standard deviation (SD), medians, Interquartile Range (IQR), percentile (P) or n (%) of individuals. (**) This could not be determined due to the occurrence of null and very low frequencies. (1) Using the Student's t test with equal variances. (2) Using Fisher's exact test. (3) Using Mann-Whitney test. BMI, body mass index; DM: diabetes mellitus; SBP: systolic blood pressure; DBP: diastolic blood pressure; SAH: systemic arterial hypertension; ART: antiretroviral therapy; AZT: zidovudine; DDI: didanosine; EFV: efavirenz; 3-TC: lamivudine; NVP: nevirapine; TDF: tenofovir.

with a correlation with this disorder, this risk factor should be evaluated in these individuals.

The association of age with a positive response to treatment was different when compared to the methods used for its assessment: while FMD displayed an improvement with treatment in the older patients, the IMT assessment did not demonstrate this difference between the groups. FMD and IMT are frequently used as surrogate measures for subclinical atherosclerosis. While IMT identifies early structural abnormalities, FMD, considered an endothelial bioassay, assesses the functional integrity of the vessel.[32] There are data demonstrating that the two methods are unique and independent and do not correlate with one other, although they are considered valid for detecting subclinical atherosclerosis. They probably reflect different aspects and stages of early atherosclerosis.[32,33] Therefore, the divergence of the results in our study is consistent with the literature and demonstrates that FMD has shown to be able to identify the benefit of using the combination of atorvastatin + aspirin in

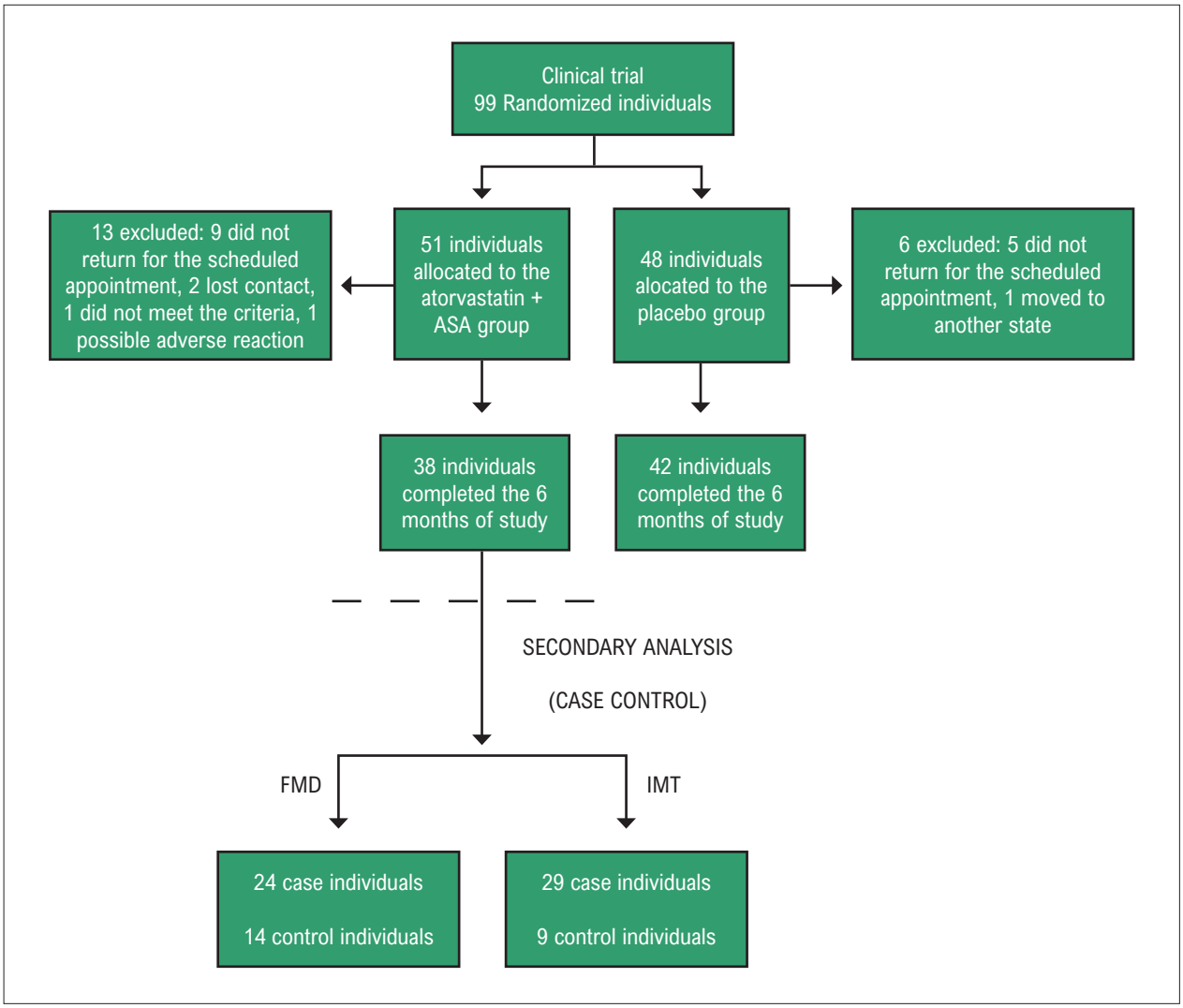


Figure 4 – *Flow chart of the study participants.*

HIV-positive individuals aged 40-59 years when compared to younger patients.

The original clinical study demonstrated a percentage reduction in LDL levels in individuals in the case group (-19.35%, p= 0.007), but without improving endothelial function. We considered some limitations in that study, and we would highlight the time receiving statins, which was planned and conducted for a duration of 6 months. Studies that have demonstrated encouraging results used statins for much longer periods than ours, thereby suggesting a path to be followed. One further question concerns the profile of the patients involved in our study. They all presented with few traditional factors of cardiovascular risk, the HIV viral load was well under control and they had been on antiretroviral treatment for several years. This selection resulted in a group of individuals with little or no inflammation, as shown by the low levels of inflammatory markers, thus revealing a population for which the short-term use of statins associated with aspirin would probably not provide any effective results.

The strong points highlighted by the present study would be the selection of individuals with low cardiovascular risk and the use of antiretroviral drugs with a low potential for causing metabolic disorders. These characteristics enable investigations into the possible effects of the drugs and the factors associated with a better outcome in an early stage of atherosclerotic disease, i.e., the period in which changes in the vascular endothelium occur, being therefore a process that can be reversed. One possible weak point, however, which should be highlighted, was the fact that the study involved a small number of individuals. The present sample may have been insufficient to detect possible associations to factors that could possibly be observed in a larger sample of individuals.

Conclusions

The study has shown that the age factor influences endothelial function improvement in subjects with HIV and low cardiovascular risk receiving a combination of atorvastatin

+ aspirin. It has also shown that FMD is a method capable of disclosing this effect. Similar studies involving a greater number of individuals are needed to confirm our hypothesis and to support the early use of the combination of atorvastatin + aspirin in subjects aged 40 to 59 years, undergoing antiretroviral treatment and with low cardiovascular risk for the prevention of cardiovascular disease.

Author Contributions

Conception and design of the research and Writing of the manuscript: Santos Junior GG, Araújo PSR, Lacerda HR, Godoi ET, Vasconcelos AF; Acquisition of data: Santos Junior GG, Leite KME, Godoi ET, Vasconcelos AF; Analysis and interpretation of the data: Santos Junior GG, Lacerda HR; Statistical analysis: Santos Junior GG; Obtaining financing: Lacerda HR; Critical revision of the manuscript for intellectual content: Araújo PSR, Lacerda HR, Godoi ET, Vasconcelos AF.

Potential Conflict of Interest

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

Sources of Funding

This study was partially funded by CNPq.

Study Association

This article is part of the thesis of master submitted by Gerson Gomes dos Santos Junior, from Universidade Federal de Pernambuco.

References

1. Oguntibeju OO. Quality of life of people living with HIV and AIDS and antiretroviral therapy. HIV AIDS (Auckl). 2012;4:117–24.
2. Nugent DB, Chowdhury M, Waters LJ. The changing face of an epidemic: healthy old age with HIV. Br J Hosp Med. 2017;78(9):516-22.
3. Trickey A, May MT, Vehreschild J, Obel N, Gill MJ, Crane H, et al. Antiretroviral Therapy Cohort Collaboration (ART-CC). Cause-specific mortality in hiv positive patients who survived ten years after starting antiretroviral therapy. PLoS ONE 2016;11(8): e0160460.
4. Tripathi A, Liese AD, Winniford MD, Jerrell JM, Albrecht H, Rizvi AA, et al. Impact of clinical and therapeutic factors on incident cardiovascular and cerebrovascular events in a population-based cohort of HIV-infected and non-HIV-infected adults. Clin Cardiol. 2014;37(9):517-22.
5. Drozd DR, Kitahata MM, Althoff KN, Zhang J, Gange SJ, Napravnik S, et al. Increased Risk of Myocardial Infarction in HIV-Infected Individuals in North America Compared With the General Population. J Acquir Immune Defic Syndr. 2017; 75(5):568-76.
6. Blum A, Shamburek R. The pleiotropic effects of statins on endothelial function, vascular inflammation, immunomodulation and thrombogenesis. Atherosclerosis. 2009;203(2):325-30.
7. Liao JK. Effects of statins on 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibition beyond low-density lipoprotein cholesterol. Am J Cardiol. 2005; 96(5A):24F-33F.
8. Dzeshka MS, Shantsila A, Lip GY. Effects of Aspirin on Endothelial Function and Hypertension. Curr Hypertens Rep. 2016;18(11):83.
9. Stein JH, Merwood MA, Bellehumeur JL, Aeschlimann SE, Korcarz CE, Underbakke GL, et al. Effects of pravastatin on lipoproteins and endothelial function in patients receiving human immunodeficiency virus protease inhibitors. Am Heart J. 2004;147(4):E18.
10. Hurlimann D, Chenevard R, Ruschitzka F, Flepp M, Enseleit F, Bechir M, et al. Effects of statins on endothelial function and lipid profile in HIV infected persons receiving protease inhibitor-containing anti-retroviral combination therapy: a randomised double blind crossover trial. Heart. 2006 Jan; 92(1): 110–2.
11. Longenecker CT, Sattar A, Gilkeson R, McComsey GA. Rosuvastatin slows progression of subclinical atherosclerosis in patients with treated HIV infection. Aids. 2016 Sep 10;30(14):2195-203.
12. Zhao J, Yan H, LI Y, Wang J, Han Li, Wang Z, et al. Pitavastatin calcium improves endothelial function and delays the progress of atherosclerosis in patients with hypercholesterolemia. J Zhejiang Univ-Sci B. (Biomed & Biotechnol). 2015; 16(5):380-7.
13. Santos Junior G, Vasconcelos A, Godoi E, Leite K, Araujo S, Lacerda H. Efeito da Atorvastatina + Aspirina na função endotelial e na inflamação em Pacientes com HIV e baixo risco cardiovascular: um Ensaio Clínico Randomizado e Duplo Cego. In: 8. Congresso Brasileiro de Ecografia Vascular; Pernambuco 5-8 setembro;2018.
14. Regattieri NAT, Leite SP, Koch HA, Montenegro CAB. Dilatação fluxo-mediada da artéria braquial: desenvolvimento da técnica, estudo em pacientes de risco para aterosclerose e em um grupo controle. Rev Bras Ultrason. 2006;9: 9–13.
15. Celermajer DS, Sorensen KE, Gooch VM,Spiegelhalter DJ, Miller OI, Sullivan ID, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. Lancet. 1992;340(8828):1111–5.
16. Freire CM, Alcântara ML, Santos SN, Amaral SS, Veloso O, Porto CL, et al, Grupo de Trabalho Do departamento de Imagem Cardiovascular da SBC. Recomendação para a quantificação pelo ultrassom da doença aterosclerótica das artérias carótidas e vertebrais. Arq Bras Cardiol Imagem Cardiovasc. 2015;28(nº especial):e1-e64.
17. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco F, Bornstein N, et al. Mannheim carotidintima-mediathickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk In: Symposia European Stroke Conferences. Brussells (Belgium), Mannheim(Germany), Hamburg (Germany), at the 13th, 15th and 20th European Stroke Conferences, Cerebrovasc Dis. 2012; 34(4):290-6.
18. Solages A, Vita JA, Thornton DJ, Murray J, Heeren T, Craven DE, et al. Endothelial function in HIV-infected persons. Clin Infect Dis. 2006 May 1;42(9):1325-32.
19. Torriani FJ, Komarow L, Parker RA, Cotter BR, Dubé MP, Fichtenbaum CJ, et al. Endothelial function in human immunodeficiency virus-infected antiretroviral-naive subjects before and after starting potent antiretroviral therapy: The ACTG (AIDS Clinical Trials Group) Study 5152s. J Am Coll Cardiol. 2008 Aug 12;52(7):569-76.
20. Jellinger PS, Yehuda H, Rosenblit P, Bloomgarden ZT, Fonseca VA, Garber AJ, et al. American Association of Cinical Endocrinologists and American College of Endocrinology. Guidelines for management of dyslipidemia and prevention of cardiovascular disease. Endocr Pract.2017;23(Suppl 2): 3.
21. Faludi AA, Izar MCO, Saraiva JFK, Chacra APM, Bianco HT, Afiune Neto A, et al. Atualização da Diretriz Brasileira de Dislipidemias e Prevenção da Aterosclerose – 2017. Arq Bras Cardiol 2017; 109(2 Supl.1):1-76.

22. Raghavan A, Rimmelin DE, Fitch KV, Zanni MV. Sex Differences in Select Non-communicable HIV-Associated Comorbidities: Exploring the Role of Systemic Immune Activation/Inflammation. Curr HIV/AIDS Rep. 2017 Dec;14(6):220-8.

23. Maggi P, Di Biagio A, Rusconi S, Cicalini S, D'Abbraccio M, d'Ettorre G, et al. Cardiovascular risk and dyslipidemia among persons living with HIV: a review. BMC Infect Dis. 2017 Aug 9;17(1):551.

24. Dubé MP, Shen C, Mather KJ, Waltz J, Greenwald M, Gupta SK. Relationship of body composition, metabolic status, antiretroviral use, and HIV disease factors to endothelial dysfunction in HIV-infected subjects. AIDS Res Hum Retroviruses. 2010 Aug;26(8):847-54

25. Ferraro S, Paolillo S, Gargiulo M, Costanzo P, Maggi P, Chirianni A, et al. [Effect of antiretroviral therapy on carotid intima-media thickness in HIV-infected patients]. G Ital Cardiol (Rome). 2009;10(9):596-601.

26. Godoi ET, Brandt CT, Lacerda HR, Godoi JT, Oliveira DC, Costa GF, et al.Intima-Media Thickness in the Carotid and Femoral Arteries for Detection of Arteriosclerosis in Human Immunodeficiency Virus-Positive Individuals.Arq Bras Cardiol. 2017 Jan;108(1):3-11.

27. Hile SJ, Feldman MB, Alexy ER, Irvine MK. Recent Tobacco Smoking is Associated with Poor HIV Medical Outcomes Among HIV-Infected Individuals in New York. AIDS Behav. 2016 Aug;20(8):1722-9.

28. Odueyungbo A, Smieja M, Thabane L, Smaill F, Gough K, Gill J, et al. Comparison of brachial and carotid artery ultrasound for assessing extent of subclinical atherosclerosis in HIV: a prospective cohort study. AIDS Res Ther. 2009 Jun 11;6:11.

29. Koethe JR, Grome H, Jenkins CA, Kalams SA, Sterling TR. The Metabolic and Cardiovascular Consequences of Obesity in Persons with HIV on Long-term Antiretroviral Therapy.AIDS. 2016 Jan 2;30(1):83-91.

30. Masiá M, Padilla S, García N, Jarrin I, Bernal E, López N, et al. Endothelial function is impaired in HIV-infected patients with lipodystrophy. Antivir Ther. 2010;15(1):101-10.

31. Freitas P, Carvalho D, Santos AC, Madureira AJ, Martinez E, Pereira J, et al. Carotid intimamedia thickness is associated with body fat abnormalities in HIV- infected patients. BMC Infect Dis. 2014 Jun 23;14:348.

32. Yan RT, Anderson TJ, Charbonneau F, Title L, Verma S, Lonn E: Relationship between carotid artery intima-media thickness and brachial artery flow-mediated dilation in middle-aged healthy men. J Am Coll Cardiol. 2005 Jun 21;45(12):1980-6.

33. Yeboah J, Burke GL, Crouse JR, Herrington DM. Relationship Between Brachial Flow - Mediated Dilation and Carotid Intima- Media Thickness in an Elderly Cohort: The Cardiovascular Health Study. Atherosclerosis. 2008 Apr; 197(2): 840–5.

For which HIV Patients Aspirin and Statins are Good?

Théo Pezel,[1,2] Layde R. Paim,[3] Otávio R. Coelho-Filho[3]

Divisão de Cardiologia, Departamento de Medicina, Universidade Johns Hopkins y,[1] Baltimore - USA
Departamento de Cardiologia, Universidade de Paris, Hospital Lariboisiere, Inserm, UMRS 942, Paris - France
Disciplina de Cardiologia, Faculdade de Ciências Médicas– Universidade Estadual de Campinas (UNICAMP), Campinas, São Paulo - Brazil
Short Editorial related to the article: The Effect of Atorvastatin + Aspirin on the Endothelial Function Differs with Age in Patients with HIV: A Case Control Study

While advances in antiretroviral treatment have revolutionized the prognosis of human immunodeficiency (HIV)-infected patients, cardiovascular complications remain the leading cause of death in these patients mainly due to an increased cardiovascular risk compared to the general population.[1] Cardiovascular prevention programs have highlighted the importance of controlling traditional risk factors in risk evaluation strategies. However, HIV-infected individuals at low cardiovascular risk have a considerable residual cardiovascular risk for events that may justify additional preventive treatment. Indeed, compared with non-HIV-infected individuals, inflammation levels are higher in HIV-infected patients, even those with viral control, and this inflammation is an important factor in the genesis of atherosclerosis.[2] Therefore, effective cardiovascular prevention strategies targeting HIV population are needed.[3] In the therapeutic arsenal of cardiovascular prevention, aspirin and statins are the cornerstones of the management of HIV-infected patients. Both drugs have pleiotropic effects, including immunomodulatory, anti-thrombogenic, and anti-inflammatory effects, that improve endothelial function and prevent the progression of carotid thickening in these patients. However, the prescription of aspirin and statins in HIV-infected patients remains largely suboptimal, with only 50% of patients adequately treated.[4] Although several studies have investigated the effects of statins and aspirin in decreasing inflammation, the results of these studies are contradictory.[5,6]

In this issue of the *Arquivos Brasileiros de Cardiologia*, Santos Jr et al.[7] report the effect of the use of a combination of atorvastatin and aspirin for six months regarding the endothelial function improvement and carotid thickness in a cohort of 38 patients with HIV infection with viral control. Improvement in endothelial function was assessed using the brachial artery flow-mediated dilation. The authors have shown a relationship between treatment response and age; a stronger response was observed in individuals older than 40 years. This result may be explained by the fact that probably older individuals had a longer exposure to inflammation caused by HIV. Several studies have shown that these same patients also have a higher cardiovascular risk due to chronic inflammation. Therefore, this study supports the prescription of a combination of atorvastatin and aspirin for the primary prevention of cardiovascular events in HIV-infected patients, particularly for those over 40 years of age. In addition, some of the findings of this study suggest that HIV-positive women may have a better response to this drug combination than men. Considering that the currently used triple therapy has a significant effect on inflammation, a mechanism intrinsically linked to the progression of atherosclerosis could explain the greater response in women than in men.

The work by Santos Jr et al.[7] is a basis for understanding the factors influencing the improvement of endothelial function in HIV-infected patients receiving atorvastatin and aspirin. Of these factors, older age appears to be one of the most important. Encouragingly, the results suggest that the combination of aspirin and statins effectively reduces or even reverses some of the deleterious effects induced by HIV. Similar studies involving a larger number of individuals are needed to confirm the authors' hypothesis and to the early use of the combination of atorvastatin and aspirin in HIV-infected patients over 40 years of age, even in those at low cardiovascular risk, for the prevention of cardiovascular disease. This study adds to the clinical evidence on positive effects of aspirin and statins in combination with antiretroviral therapy in HIV patients, after due consideration of possible drug interactions. The results presented by Santos Jr et al.[7] provide a fascinating basis for these considerations; however, it is essential to highlight some important limitations of the study. First, the study was not a randomized clinical trial and the exposure to statins was relatively short compared to other studies. In addition, it included a cohort of patients with HIV with a low cardiovascular risk profile and low inflammation as confirmed by the low levels of inflammatory markers. Importantly, the impact of aspirin and statins on vascular remodeling of HIV patients with this clinical profile may not be relevant.

Keywords

HIV; HIV/infection; Anti-HIV Agents/therapeutic use; Cardiovascular Diseases/complications; Mortality; Risk Factors; Aspirin; Statins; Atherosclerosis; Endothelium

Mailing Address: Otávio Rizzi Coelho-Filho •
Disciplina de Cardiologia, Faculdade de Ciências Médicas, Hospital das Clínicas, Universidade Estadual de Campinas, UNICAMP - Rua Vital Brasil. 251. Postal Code 13083-888, Cidade Universitária "Zeferino Vaz", Campinas, SP - Brazil
Email: orcfilho@unicamp.br, tavicocoelho@gmail.com

DOI: https://doi.org/10.36660/abc.20210560

References

1. Salmazo PS, Bazan SGZ, Shiraishi FG, Bazan R, Okoshi K, Hueb JC. Frequency of Subclinical Atherosclerosis in Brazilian HIV-Infected Patients. Arq Bras Cardiol. 2018;110(5):402–10.
2. Leite KME, Santos Júnior GG, Godoi ETAM, Vasconcelos AF, Lorena VMB, Araújo PSR, et al. Inflammatory Biomarkers and Carotid Thickness in HIV Infected Patients under Antiretroviral Therapy, Undetectable HIV-1 Viral Load, and Low Cardiovascular Risk. Arq Bras Cardiol. 2020;114(1):90–7.
3. Kengne AP, Ntsekhe M. Challenges of Cardiovascular Disease Risk Evaluation in People Living With HIV Infection. Circulation. 2018;137(21):2215–7.
4. De Socio GV, Ricci E, Parruti G, Calza L, Maggi P, Celesia BM, et al. Statins and Aspirin use in HIV-infected people: gap between European AIDS Clinical Society guidelines and clinical practice: the results from HIV-HY study. Infection. 2016;44(5):589–97.
5. Hürlimann D, Chenevard R, Ruschitzka F, Flepp M, Enseleit F, Béchir M, et al. Effects of statins on endothelial function and lipid profile in HIV infected persons receiving protease inhibitor-containing anti-retroviral combination therapy: a randomised double blind crossover trial. Heart Br Card Soc. 2006;92(1):110–2.
6. Longenecker CT, Sattar A, Gilkeson R, McComsey GA. Rosuvastatin slows progression of subclinical atherosclerosis in patients with treated HIV infection. AIDS Lond Engl. 2016;30(14):2195–203.
7. Santos Junior GG, Araújo PSR, Leite KME, Godoi ET, Vasconcelos AF, Lacerda HR. The Effect of Atorvastatin + Aspirin on the Endothelial Function Differs with Age in Patients with HIV: A Case- Control Study. Arq Bras Cardiol. 2021; 117(2):365-375. doi: https://doi.org/10.36660/abc.20190844

Arterial Hypertension and Serum Uric Acid in Elderly- SEPHAR III Study

Roxana Buzas,[1] Vlad-Sabin Ivan,[1] Oana-Florentina Gheorghe-Fronea,[2] Adina Flavia Morgovan,[1] Melania Ardelean,[1] Nicolae Albulescu,[1] Maria Dorobantu,[2] Daniel Florin Lighezan[1]

University of Medicine and Pharmacy Victor Babes Timisoara - Department of Internal Medicine,[1] Timisoara – Romania
Carol Davila University of Medicine and Pharmacy - Cardio-Thoracic Pathology Department,[2] Bucuresti – Romania

Abstract

Background: Hyperuricemia is a frequent finding in patients with arterial hypertension, and there is increasing evidence that this entity is also a risk factor for cardiovascular disease.

Objective: In the context of an aging population, this study aims to evaluate serum uric acid levels and arterial hypertension prevalence and control in a subgroup of Romanian adults (>65 years), concerning the influence of age on these parameters.

Method: The study sample consists of 1,920 adults included in SEPHAR III survey, of whom 447 were elderly patients (>65 years of age). During the two study visits, three blood pressure (BP) measurements were performed at 1-min intervals and serum uric acid levels, kidney function by estimated glomerular filtration rate, blood pressure, and intima media thickness measurements were conducted. Hypertension and controls were defined according to the current guidelines. Intima-media thickness evaluation was assessed by B-mode Doppler ultrasound evaluation. A significance level $p < 0.05$ was adopted for the statistical analysis.

Results: Adult patients had a significant lower serum uric acid levels, compared to elderly patients, regardless of glomerular filtration rate levels. Adult patients showed a significantly lower intima-media thickness levels, when compared to elderly patients.

Conclusion: Similar to previous studies, in the present study, age represented one of the factors contributing to the increased level of serum uric acid. An increasing prevalence of arterial hypertension with age, together with a poor control of blood pressure, was also obtained.

Keywords: Hypertension; Uric Acid; HYperuricemia; C-Effectardiovascular Diseases; Glomerular Filtration; Age-Effect.

Introduction

Life expectancy continues to increase in developed countries worldwide, leading to an ever-increasing representation of older adults (people over 65 years of age) within the population.[1]

According to the Eight Report of the Joint National Committee (JNC 8), approximately 970 million people worldwide have high blood pressure. It is estimated that by 2025, 1.56 billion adults will be living with arterial hypertension (HT). The etiology of essential HT still remains unknown; its pathogenesis includes multiple genetic and environmental factors. More than two-thirds of individuals over 65 years of age suffer from HT, according to the Seventh Report of the Joint National Committee (JNC-7).[2] Several epidemiological studies indicated that the incidence of HT and related cardiovascular disease is higher in the elderly than in the young population.[2,3] A study on its prevalence and control among United States adults from 1999 to 2004 showed that the prevalence of HT has more than doubled in the elderly than in the young population. Even if the general belief is that HT is an aging disorder, in recent years, the middle-aged population has shown an increase in the incidence of arterial hypertension.

On the other hand, hyperuricemia is more common, and several studies show that serum uric acid levels are linked to an increase in the prevalence of hypertension (HT), which also contributes to a lack of optimal blood pressure (BP) control.[4]

SEPHAR (Study for the Evaluation of Prevalence of Hypertension and Cardiovascular Risk in Romania) is a project that aims to evaluate the prevalence of HT and other related factors including serum uric acid. To date, three separate SEPHAR studies have been conducted at several years intervals, with SEPHAR II being conducted in 2012, which was the first to evaluate the serum uric acid levels, which also correlated the serum uric acid (SUA) levels with intima media thickness, renal function, and cardiovascular risk. Continuing with SEPHAR III in 2016, which provided further data on SUA levels and its relationship with HT prevalence in Romania, several other indices were also used, such as

Mailing Address: Vlad-Sabin Ivan •
Universitatea de Medicină şi Farmacie Victor Babes din Timişoara -
P-ta Eftimie Murgu nr 1 Timisoara 300041 – Romania
E-mail: vlad_sabin_ivan@yahoo.com
Manuscript received January 14, 2020, revised manuscript August 03, 2020, accepted August 16, 2020

DOI: https://doi.org/10.36660/abc.20200004

eGFR and echocardiographic parameters. SEPHAR III was designed as a cross-sectional survey for characterizing data for the adult population in Romania for HT prevalence, control, and antihypertensive agents.[5,6]

This paper aims to evaluate SUA levels, IMT and HT prevalence, and control, in a group of Romanian adults, concerning the aging population.

Material and methods

A mobile medical caravan dubbed SEPHAR Bus was used to perform two visits, at a 4-day interval between them. Overall, 1,920 Romanian adults were enrolled in this SEPHAR III survey (mean age 48.63 years, 52.76% females), of whom 447 were elderly patients (23.28%, 65 years of age or older). Patients were examined and three BP measurements, in accordance with the current European Guidelines for BP monitoring, were performed at one-minute intervals while sitting. During each visit, three sitting BP measurements, with an automated BP measurement device (OMRON M6), were registered. The cuff was adjusted for the arm's circumference, and all of the measurements were performed on the same arm that presented the highest BP values during the inaugural visit.

A systolic blood pressure (SBP) of more than 140mmHg and/or diastolic blood pressure (DBP) greater than 90mmHg in both visits was considered HT, using the average of the second and third BP values of each visit. The first BP of each visit was not taken into consideration for further analysis. Moreover, known and treated HT, with controlled or uncontrolled BP during the previous two weeks, was also taken into consideration.

For a subject to have controlled BP, 2018 ESH-ESC guidelines on hypertension was used, defining a BP control for hypertensive subjects with at least two weeks of prior treatment, an SBP and a DBP of less than 140mmHg and 90mmHg, respectively.

Blood sample analysis that included the aforementioned SUA was performed during the second visit, with the patient being informed in the first visit that a fasting period of at least 8 hours would be required. SUA levels were analyzed with a COBAS 6000 analyzer with uricase/peroxidase reagents, with normal values given between 2.4 to 5.70mg/dl in females and 3.40 to 7.00mg/dl in males. Hyperuricemia was diagnosed when above normal ranges were identified. For the evaluation of the kidney function, both Modification of Diet in Renal Disease formula (MDRD) and Chronic Kidney Disease Epidemiology Collaboration formula (CKD-EPI) values were calculated and used in the statistical analysis.

A portable echocardiograph (model General Electric Vivid Q), which automatically calculated the intima-media thickness (IMT) of each distal wall of the common carotid artery, 1 cm below the carotid bulb, was used. The IMT was measured using a linear probe with an adjustable frequency between 7.5 and 10 MHz.

The Ethics Committee of the "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania, approved the study in complete accordance with the Declaration of Helsinki and written consent was required from all participants before any examination was undertaken.

Statistical analysis

Results for targeted variables were presented, using counts with corresponding percentages for categorical data and descriptive statistics (mean, standard deviation) for continuous data. Differences in means for continuous variables were analyzed using t-tests for independent samples, while Chi-squared test was used to examine differences between categorical variables. Considering the sample size normality was assumed for all data, and the Spearman correlation test was used, as we were interested in some correlations in some categorical and binary data. Analyses of covariance (ANCOVA) were used to investigate the effects of SUA on normotensive and hypertensive elderly patients, with controls for the confounding variables and risk factors: age, gender, and BMI. Similarly, ANCOVA was considered to assess the effect of IMT levels and eGFR levels (assessed both by MDRD and by CKD-EPI formula) on SUA levels considering normouricemia and hyperuricemia elderly patients.

Statistical analysis was performed with a significance level of 5%. The IBM SPSS Statistics, version 20.0, software for Windows was used. Descriptive statistics, figures, and tables were considered to summarize our results.

Results

A total of 1,920 adult patients (18 years of age or older) were included in the analysis, of whom 447 were elderly patients (65 years of age or older, 23.28%). Table 1 summarizes baseline characteristics of the analyzed patients, and Table 5 summarizes the baseline anthropometric characteristics of the population.

Significant statistical difference was found among the proportion of hypertensive patients in the two studied groups. HT was more frequent in the elderly group ($p<0.001$). Considering controlled HT values, only 42 patients (13.95%) of the 301 hypertensive patients included in the elderly group seem to have controlled BP values. A significantly statistical higher proportion of patients with controlled HT was identified in the adult group when compared to the elderly group, considering only hypertensive patients ($p<0.001$).

Analyzing the SUA values, a significant difference was obtained in the mean value of SUA in the two groups. Adult patients presented significantly lower SUA levels, on average, with 0.51mg/dl, as compared to elderly patients (4.89 mg/dl vs. 5.40mg/dl, $p<0.001$).(Figure 1)

When studying SUA levels by groups of normotensive and hypertensive elderly patients, the highest values were observed in hypertensive elderly patients, these values being significantly higher when compared to those recorded in normotensive elderly patients. The differences remained after adjusting for age, sex, and BMI (Table 2). Hypertensive elderly patients compared to normotensive elderly patients had significantly higher SUA levels, on average, with 0.39 mg/do (5.53 mg/dL vs. 5.14 mg/dL, $p=0.008$).

However, SUA levels in hypertensive elderly patients did not change regarding the HT control status, $p=0.632$). Only 1,059 of the 1,473 adult patients and 338 of the 447 elderly patients had their IMT values measured. A significant

Table 1 (*) – Comparison between studied parameters of patients based on age (baseline characteristics)

	Adult Patients (N=1473)	Elderly Patients (N=447)	p-Value
Categories for blood pressure			
Normotensive	894 (60.69%)	146 (32.66%)	<0.001
Hypertensive	579 (39.31%)	301 (67.34%)	
Hypertension – including only hypertensive patients (#)			
Under control	154 (26.60%)	42 (13.95%)	<0.001
Not under control	425 (73.40%)	259 (86.05%)	
SUA (mg/dl)			
N	1473	447	<0.001
Mean (SD)	4.89 (1.293)	5.40 (1.479)	
IMT (mm)			
N	1059	338	<0.001
Mean (SD)	0.60 (0.124)	0.80 (0.140)	
$eGFR_{MDRD}$			
N	1473	447	<0.001
Mean (SD)	85.51 (17.623)	69.36 (18.134)	
$eGFR_{CKD-EPI}$			
n	1473	447	<0.001
Mean (SD)	94.47 (17.347)	69.82 (16.876)	

** p-values are obtained with independent sample t-tests (*) and with Chi-square tests. Continuous data (*) are summarized as mean (standard deviation patients).*

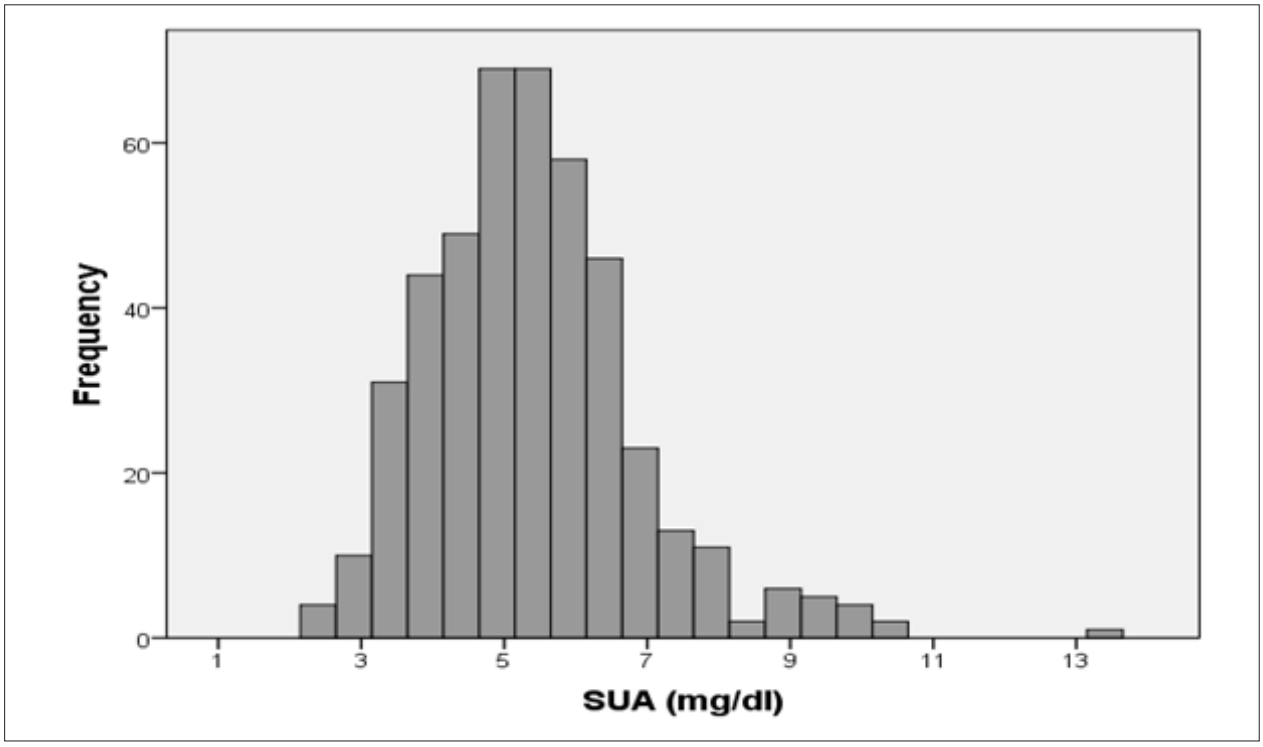


Figure 1 – *Distribution of the SUA values in the elderly patients' group*. SUA- serum uric acid.*

Table 2 – Serum uric acid by groups of normotensive and hypertensive elderly patients

	Normotensive Elderly Patients (N=146)	Hypertensive Elderly Patients (N=301)	p-Value
Unadjusted	5.14 (0.122)	5.53 (0.085)	0.008
Adjusted for age	5.13 (0.122)	5.53 (0.085)	0.007
Adjusted for gender	5.12 (0.118)	5.53 (0.082)	0.005
Adjusted for BMI	5.17 (0.121)	5.51 (0.084)	0.021

** Notes: p-values are obtained with ANCOVA test; values are summarized as mean (standard error). BMI: body mass index.*

difference in mean value of IMT was obtained with lower IMT levels in adult patients, on average, with 0.20mm, as compared to elderly patients $p<0.001$). When considering only the elderly group, no significant differences were found in IMT values when considering SUA levels ($p=0.510$) (Table 3)

Significant differences in the mean value of $eGFR_{MDRD}$ were obtained; adult patients presented significantly higher $eGFR_{MDRD}$ levels, on average, with 16.15 ml/min/1.73m², as compared to elderly patients ($p<0.001$). The same results were obtained when using $eGFR_{CKD-EPI}$. Adult patients presented significant higher $eGFR_{CKD-EPI}$ levels, on average, with 24.65 ml/min/1.73m², as compared to elderly patients ($p<0.001$) (Table 1). When considering only the elderly group, the lower values of the estimated glomerular filtration rate (eGFR), assessed by both MDRD and CKD-EPI formulas, were observed in elderly patients with hyperuricemia, with these values being significantly lower than eGFR levels recorded in elderly patients with normouricemia. All of these differences remained statistically significant after adjusting for age, sex, and BMI (Table 4).

Discussion

HT is a highly prevalent condition that dramatically rises in incidence with increasing age. According to JNC, hypertension occurs in more than two-thirds of individuals after 65 years of age.[2] Moreover, data from the Framingham Heart Study, in men and women free of hypertension at 55 years of age, indicate that the remaining lifetime risks for development of hypertension through 80 years of age are 93% and 91%, respectively.[7] More than 90% of all individuals who are free of hypertension at 55 years of age will develop it during their remaining lifespan. As expected, the prevalence of HT in the elderly group was significantly higher.

The effect of age on hypertension control still seems to be controversial. A Serial Cross-sectional study of age differences in the control of HT in US Physician's Offices, from 2003-2010, suggests that older patients were more likely to achieve hypertension control when compared to younger patients, which is the same as findings from NAMCS but in contrast with the National Health and Nutrition Examination Survey.[8,9]

SEPHAR III results revealed that elderly Romanian patients have a reduced percentage of controlled HT (13.95%) that is significantly lower when compared to the adult group. Suboptimal hypertension control in older patients may be related to poor management, culinary habits, or less aggressive treatment, using, with fewer medications or lower doses than their younger counterparts.

SUA levels are strongly correlated with aging. SEPHAR III data reconfirms SUA increased values in the population of >65 years and especially in HT patients. As expected, elderly patients had an increased IMT. Although previous studies showed a correlation between IMT values and SUA levels, our analysis, which considered only patients aged >65 years, revealed no significant differences in IMT among SUA subgroups after adjusting for age.[7] These results are consistent with previous studies suggesting that the relationship between SUA and plaque was nonexistent or very weak and easily influenced by other factors.[10,11]

The association between hyperuricemia and chronic kidney disease was presented above.[12] Among elderly patients, SUA values were significantly increased, regardless of renal function, which is the same as data from a Japanese study with elderly women.[13] SEPHAR III results suggest that age and SUA have a synergistic effect on BP status, regardless of conventional cardiovascular risk factors.

The present study has some limitations, such as the impact of ongoing treatment for chronic diseases on the levels of serum uric acid. The patients were questioned on their current medications and whether they are adherent to therapy, but earlier medications were not documented. To establish such a relationship, we consider that two visits, with intervals of several days between them, were not enough to quantify the impact of such interventions. This analysis is also part of a larger study that encompassed adults of 18 years of age or over; therefore, the proportion of elderly patients is lower, which could limit its power to characterize this age group.

Recent papers on the risk of hyperuricemia have also stressed the increased association between the levels of serum uric acid and cardiovascular disease. The Uric Acid Right for Heart Health (URRAH) study of over 22,000 subjects showed, through multivariate Cox regression analyses, that the serum uric acid is an independent risk factor for mortality.[14]

Other studies evaluated the effect of serum uric acid on arterial stiffness in hypertensive patients and found no influence on the progression of pulse wave velocity in the studied population after a median follow-up of 3.8 years. The authors of this study[15] evaluated 422 adult hypertensive patients and showed, in an unadjusted population, significant association between vessel rigidity and serum uric acid, but the significance was lost when adjusted for different parameters for example such as BMI.

Table 3 – Serum uric acid by groups of normotensive and hypertensive elderly patients

	Normouricemia Elderly Patients (N=356)	Hyperuricemia Elderly Patients (N=91)	p-Value
Patients included in the analysis (*)	262	76	
Unadjusted	0.80 (0.009)	0.82 (0.016)	0.373
Adjusted for age	0.80 (0.008)	0.81 (0.015)	0.510
Adjusted for gender	0.80 (0.009)	0.82 (0.016)	0.119
Adjusted for BMI	0.80 (0.009)	0.82 (0.016)	0.380

** Notes p-values are obtained with ANCOVA test, values are summarized as mean (standard error). (*) Analyses based on patients with measured IMT values.*

Table 4 – Serum uric acid levels and renal function by groups of normouricemia and hyperuricemia elderly patients

	Normouricemia Elderly Patients (N=356)	Hyperuricemia Elderly Patients (N=91)	p-Value
$eGFR_{MDRD}$			
Unadjusted	71.50 (0.936)	61.01 (1.851)	<0.001
Adjusted for age	71.43 (0.919)	61.25 (1.818)	<0.001
Adjusted for gender	71.50 (0.938)	61.00 (1.862)	<0.001
Adjusted for BMI	71.49 (0.938)	61.05 (1.866)	<0.001
$eGFR_{CKD-EPI}$			
Unadjusted	71.86 (0.869)	61.83 (1.719)	<0.001
Adjusted for age	71.78 (0.832)	62.17 (1.646)	<0.001
Adjusted for gender	71.92 (0.870)	61.59 (1.727)	<0.001
Adjusted for BMI	71.91 (0.871)	61.66 (1.733)	<0.001

** Notes: p-values are obtained with ANCOVA test, values are summarized as mean (standard error).*

Table 5 – Comparison between main baseline and anthropometric characteristics between adult and elderly patients

	Adult patients (N=1473)	Elderly patients (N=447)	p-value
BMI (kg/m^2)(*) n Mean (SD)	 1473 27.70 (5.892)	 447 29.91 (5.157)	<0.001
IMT (mm) n Mean (SD)	 1059 0.60 (0.124)	 338 0.80 (0.140)	<0.001

SD: standard deviation; BMI: body mass index.

A different analysis regarding Central and Eastern Europe has also shown an increased prevalence of hyperuricemia in hypertensive patients with at least one quarter of the studied population having increased levels of serum uric acid. In the covariate analysis with cardionephrometabolic variables, of the 3,206 patients from the BP-CARE study, the only significant relationship between serum uric acid levels was found to be with chronic kidney disease.[16]

There are also several other studies that show a link between the levels of SUA and other metabolic parameters, such as LDL-cholesterol, showing a relationship between these two as regards the risk of developing hypertensions in the latter stages of life.[17] In the elderly, there are other studies that support the finding that SUA is often found in metabolic syndrome, such as the report from the authors of Brisighella Heart Study.[18] In our analysis, a significant difference was found between the elderly versus adult patients, with elderly patients being more obese and having a higher IMT.

Whether the serum uric acid has a minor effect on vessel rigidity, acts synergistically with other risk factor, or has no effect at all is still a debate that needs to be answered, but hyperuricemia should be treated nonetheless.

Conclusion

Our study is the first of its kind that provides specific data of HT and SUA values focused on Romanian elderly patients. Although it is increasingly recognized that biological rather than chronological age is important, HT treatment and control in older populations must be optimized, considering individual health characteristics, since therapy reduces mortality, stroke, and heart failure. Our study serves to emphasize that increased SUA levels are associated with aging and correlations with HT are identified, regardless of the state of renal function.

Author Contributions

Conception and design of the research, Statistical analysis and Writing of the manuscript: Buzas R, Vlad-Sabin I; Acquisition of data: Morgovan AF, Ardelean M, Albulescu N; Analysis and interpretation of the data: Buzas R, Vlad-Sabin I; Critical revision of the manuscript for intellectual contente: Gheorghe-Fronea OF, Dorobantu M, Lighezan DF.

Potential Conflict of Interest

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

Sources of Funding

This study was partially funded by Romanian Society of Hypertension and Servier Pharma Romanian Subsidiary through a non-restrictive research grant.

Study Association

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

References

1. Roberts L. 9 Billion. Science. 2011;333(6042):540-3.
2. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr JL, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension. 2003;42(6):1206-52.
3. Rosano C, Watson N, Chang Y, Newman AB, Aizenstein HJ, Du Y, et al. Aortic pulse wave velocity predicts focal white matter hyperintensities in a biracial cohort of older adults. Hypertension. 2013;61(1):160-5.
4. Valaiyapathi B, Siddiqui M, Oparil S, Calhoun DA, Dudenbostel T. High uric acid levels correlate with treatment- resistant hypertension. Hypertension. 2017;70(suppl 1):AP550.
5. Buzas R, Tautu OF, Dorobantu M, Ivan V, Lighezan D. Serum uric acid and arterial hypertension—Data from Sephar III survey PLoS One. 2018;13(7):e0199865.
6. Dorobantu M, Tautu OF, Dimulescu D, Sinescu C, Gusbeth-Tatomir P, Arsenescu-Georgescu C, et al. Perspectives on hypertension's prevalence, treatment and control in a high cardiovascular risk East European country: data from the SEPHAR III survey. J Hypertens. 2018;36(3):690-700.
7. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KK. The progression from hypertension to congestive heart failure. JAMA. 1996;275(20):1557-62.
8. Ma J, Stafford RS. Screening, treatment and control of hypertension in US private physician offices, 2003-2004. Hypertension. 2008;51(5):1275-81.
9. Gu A, Yue Y, Argulian E. Age differences in treatment and control of hypertension in US physician offices, 2003-2010: a serial cross-sectional study. Am J Med. 2016;129(1):50-8.
10. Pan WH, Bai CH, Chen JR, Chiu HC. Associations between carotid atherosclerosis and high factor VIII activity, dyslipidemia, and hypertension. Stroke. 1997;28(1):88-94.
11. Herder M, Arntzen KA, Johnsen SH, Mathiesen EB. The metabolic syndrome and progression of carotid atherosclerosis over 13 years. The Tromsø study. Cardiovasc Diabetol. 2012 Jun;11:77.
12. Buzas R, Tautu OF, Dorobantu M, Ivan V, Lighezan D. Serum uric acid and arterial hypertension - data from Sephar III survey. PLoS One. 2018;13(7):e0199865.
13. Kawamoto R, Tabara Y, Kohara K, Kusunoki T, Abe M, Miki T. Synergistic Influence of age and serum uric acid on blood pressure among community-dwelling Japanese women. Hypertens Res. 2013;36(7):634-8.
14. Virdis A, Masi S, Casiglia E, Tikhonoff V, Cicero AFG, Ungar A, et al. Identification of the uric acid thresholds predicting an increased total and cardiovascular mortality over 20 years. Hypertension. 2020;75(2):302-8.
15. Maloberti A, Rebora P, Andreano A, Vallerio P, Chiara B, Signorini S, et al. Pulse wave velocity progression over a medium-term follow-up in hypertensives: focus on uric acid. J Clin Hypertens (Greenwich). 2019;21(7):975-83.
16. Redon P, Maloberti A, Facchetti R, Redon J, Lurbe E, Bombelli M, et al. Gender-related differences in serum uric acid in treated hypertensive patients from central and east European countries: findings from the blood pressure control rate and cardiovascular risk profile study. J Hypertens. 2019;37(2):380-8.
17. Cicero AFG, Fogacci F, Giovannini M, Grandi E, D´Addato S, Borghi C, et al. Interaction between low-density lipoprotein-cholesterolaemia, serum uric level and incident hypertension: data from the Brisighella Heart Study. J Hypertens. 2019;37(4):728-31.
18. Cicero AFG, Fogacci F, Giovannini M, Grandi E, Rosticci M, D´Addato S, et al. Serum uric acid predicts incident metabolic syndrome in the elderly in an analysis of the Brisighella Heart Study. Sci Rep. 2018;8(1):11529.

Type 1 Cardiorenal Syndrome in Decompensated Heart Failure Patients in a Low-Income Region in Brazil: Incidence of Acute Kidney Injury (AKIN and KDIGO Criteria), Need for Dialysis and Mortality

Ginivaldo Victor Ribeiro do Nascimento,[1,2] Heitor Carlos Domingues de Brito,[2] Carlos Eduardo Batista de Lima,[3,4]

Universidade Estadual do Piauí,[1] Teresina, PI - Brazil

Faculdade Integral Diferencial Curso de Medicina,[2] Teresina, PI - Brazil

Universidade Federal do Piauí, Centro de Ciências da Saúde,[3] Teresina, PI - Brazil

Centro de Pesquisa CARDIOLIMA,[4] Teresina, PI - Brazil

Abstract

Background: **Type 1 cardiorenal syndrome is associated with higher mortality in heart failure patients. However, few studies have compared the diagnostic criteria of acute kidney injury (AKI) in this population.**

Objective: **To assess clinical and functional features and factors associated AKI in patients with heart failure.**

Methods: **Retrospective, cohort study on patients with decompensated heart failure or recent acute myocardial infarction, conducted in a tertiary hospital in a low-income region of Brazil. Clinical, laboratory and echocardiographic features were compared between patients with and without AKI according to the Acute Kidney Network (AKIN) and Kidney Disease: Improving Global Outcomes (KDIGO) criteria. The level of statistical significance was set at $p < 0.05$.**

Results: **Of 81 patients, 61.73% had AKI. Mean creatinine and urea levels were 1.79±1.0 mg/dL and 81.5±46.0 mg/dL, respectively, and higher in the group with AKI ($p < 0.05$). No evidence of a relationship between cardiac changes and reduced renal function. Chronic renal disease was associated with higher prevalence of AKI. Higher mortality was observed in patients with AKI than in patients without AKI (32.0% vs. 9.8%, $p = 0.04$, OR 8.187 ad 95% confidence interval 1.402-17.190, $p = 0.020$).**

Conclusion: **In this population of patients with heart failure, AKI was highly prevalent and considered an independent risk factor for mortality. Cardiac changes were not associated with AKI, and the KDIGO and AKIN criteria showed similar performance.**

Keywords: **Cardio-Renal Syndrome/complications; Renal Insufficiency; Acute Kidney, Injury/standards(AKIN); Kidney Disease Improving Global Outcome/standards(KDIGO).**

Introduction

Cardiorenal syndrome (CRS) encompasses various acute and chronic conditions in which dysfunction in one organ (either the heart or kidneys) implicates dysfunction in the other.[1,2] Approximately one third of patients with heart failure (HF) decompensation may also develop acute renal function impairment, which is characterized as type 1 CRS.[3]

Ventricular dysfunction can cause negative effects on renal function and, meanwhile, renal insufficiency may significantly impair cardiac function. Direct and indirect effects of each dysfunctional organ can initiate and mutually perpetuate a combined set of disorders.[2]

In the last decades, the term "acute kidney injury" (AKI) has been revised, with emphasis on a progressive pathophysiological process that may be noticeable by the presence of small changes in markers of renal injury, especially creatinine. On this regard, two diagnostic criteria have been proposed, the Acute Kidney Network (AKIN) and the Kidney Disease: Improving Global Outcomes (KDIGO).[1,4] The former, developed to harmonize previous definitions and criteria, distinguish from the term "worsening of renal function", and have been widely used in investigations of AKI and CRS.[1,4,5] Few studies in the literature have evaluated these AKI and CRS criteria, particularly in emerging countries and low index of economic development.[6,7]

The aim of the present study was to compare the incidence of CRS using the AKIN and the KDIGO criteria, and to assess risk factors for CRS, need for dialysis, and mortality in patients with decompensated HF.

Methods

This was an observational, retrospective, cohort study conducted in a tertiary referral hospital for urgency and emergency care in Teresina, Brazil – the *Hospital de Urgências de Teresina*. All patients with a history of heart disease admitted

Mailing Address: Carlos Eduardo Batista de Lima •
Rua General Lages, 1555, Apto. 402; Edifício La Concorde.
Postal Code 64048-350, Fátima, Teresina, PI - Brazil
E-mail: carlos.lima@ufpi.edu.br
Manuscript received February 06, 2020, revised manuscript July 31, 2020, accepted August 16, 2020

DOI: https://doi.org/10.36660/abc.20200097

with decompensated HF, and patients with recent acute myocardial infarction (AMI) with echocardiographic evidence of reduced ejection fraction (<55%) were included in the study. Patients younger than 18 years, kidney transplanted patients, patients on chronic dialysis and those without at least two creatinine measurements performed during hospitalization were excluded.

This study was reviewed and approved by the local ethics committee (CAAE n. 54207914.5.0000.5211). Data were obtained by reviewing medical records and echocardiographic findings of patients hospitalized from 01 January to 31 December 2014. The variables studied included admission date and diagnosis, age, sex, comorbidities –systemic arterial hypertension (SAH), diabetes mellitus (DM), dilated cardiomyopathy, cerebrovascular disease, chronic renal disease (CRD), liver disease – laboratory parameters (creatinine, urea, potassium, bicarbonate, pH), clinical improvement, hospital discharge and death.

AKI was defined based on changes in creatinine levels, following the two diagnostic criteria (AKIN and KDIGO). The AKIN proposes a diagnosis of AKI based on change between two creatinine values within a 48-hour period, and need for renal replacement therapy. An absolute increase in serum creatinine greater than 0.3 mg/dL or a 1.5-1.9 times baseline is classified as stage 1 AKI. An increase 2.0–3.0 times baseline is classified as stage 2 AKI. Patients with increase in serum creatinine 3.0 times baseline or serum creatinine levels equal to or greater than 4.0 mg/dl (abrupt rise of at least 0.5 mg/dL) or initiation of renal replacement therapy are classified as stage 3 AKI.[8,9]

According to the KDIGO criteria, an increase in serum creatine 1.5 times baseline within seven days or an increase by 0.3 mg/dL within 48 hours is classified as stage 1, an increase equal to or greater than 2 times baseline is classified as stage 2, and stage 3 is considered an increase in serum creatinine 3 times baseline (to ≥4 mg/dL) or on renal replacement therapy.[4]

Statistical analysis

Continuous variables were expressed as mean and standard deviation, according to normality of data distribution verified by the Kolmogorov-Smirnov test, and compared using the unpaired Student's t-test. Categorical variables were expressed as proportions and compared by Pearson chi-square test. The combined effect of predictive variables on the response variable was assessed using multiple logistic regression models with adjusted odds ratio (OR). The variables that showed a trend for an association ($p<0.2$) in the bivariate analysis were added in the regression model, and those with statistically significance association ($p< 0.05$) were maintained in the model. The final multiple logistic regression model was adjusted using the Enter model. The Hosmer–Lemeshow test, a statistical test for goodness of fit for logistic regression models, showed that the final model was adequate to explain the response variable. The variance inflation factor (VIF) was used to assess multicollinearity among the independent variables, and a VIF cutoff of 4 was adopted to identify multicollinearity. However, the test did not detect multicollinearity among the variables studied. A significance level of 5% was set for all the statistical tests. Data were analyzed using the R-Project software, version 3.0.2, and the Statistical Package for the Social Science (SPSS), version 20.0.

Results

A total of 81 patients admitted for compensated HF or recent AMI were included in the study. Clinical and demographic characteristics of patients are described in Table 1. Mean age of patients was 67.02 ± 14.97 years, and 43 patients (53.1%) were men. The diagnosis of decompensated HF was more common in patients with previous heart disease, and SAH was the most common comorbidity.

The study population was divided into three subgroups, according to the presence or not of AKI. Clinical, laboratory and echocardiographic features of these patients (50 with AKI and 32 without AKI) are described in Table 2. Although no differences in clinical variables were observed between the two groups, most patients with AKI had renal disease and elevated levels of urea and creatinine.

Regarding the association of cardiac and echocardiographic features with development of kidney injury, HF was the main admission diagnosis among patients with altered renal function. No relationship was found between reduced ejection fraction and development of CRS.

With respect to in-hospital mortality, while a 9.7% rate was found in patients without AKI, 32% of patients with AKI

Table 1 – General characteristics of patients with heart failure (ischemic and non-ischemic) evaluated for the presence of acute kidney injury (n = 81)

Variable	N
Age (years)	67.02 ± 14.97
Mean ± SD	
Sex (%)	43 (53.09)
Male	
Diagnosis (%)	
Recent AMI	16 (19.75)
HF with a history of heart disease	62 (76.55)
History of HF and recent AMI	3 (3.7)
Other diagnoses*	8 (9.88)
Comorbidities (%)	
SAH	48 (59.26)
DM	26 (32.1)
CRD	20 (24.69)
Cerebrovascular disease	7 (8.64)
Liver disease	6 (7.41)
Others	24 (29.63)

*AMI: acute myocardial infarction; HF: heart failure; SAH: systemic arterial hypertension; DM: diabetes mellitus; CRD: chronic renal disease; SD: standard deviation. * Patients with decompensated heart failure and left ventricular ejection fraction < 55% without a history of heart disease or recent acute myocardial, arrhythmias, hypertensive pulmonary edema or infections.*

Table 2 – Clinical, laboratory and echocardiographic features, and clinical outcomes of patients with and without acute kidney injury of hospitalized patients with heart failure or acute myocardial infarction (n = 81)

Variables	Without AKI (n = 31)	With AKI (n = 50)	OR (95%CI)	p – value
Clinical data				
Age (± SD)	64.03 ± 16.08	68.88 ± 14.08	1.02 (0.99-1.05)	0.172
Male sex – n (%)	20 (64.52)	23 (46)	2.13 (0.85-5.37)	0.104
SAH – n (%)	15 (48.39)	33 (66)	0.48 (0.20-1.20)	0.116
DM – n (%)	8 (25.81)	18 (36)	0.62 (0.23-1.66)	0.339
CRD – n (%)	1 (3.23)	19 (38)	18.4 (2.31-146.10)	**0.001**
Cerebrovascular disease - n (%)	1 (3.23)	6 (12)	4.09 (0.47-35.73)	0.337
Liver disease – n (%)	3 (9.68)	3 (6)	0.60 (0.11-3.16)	0.858
Others– n (%)	7 (22.58)	17 (34)	–	–
Laboratory data (± DP)				
Urea (mg/dL)	46.65 ± 25.66	81.52 ± 46.04	1.03 (1.01-1.05)	**0.001**
Creatinine (mg/dL)	1.17 ± 0.76	1.79 ± 0.97	1.02 (1.01-1.04)	**0.002**
Potassium (mEq/L)	4.11 ± 0.75	4.4 ± 1.02	2.76 (1.29-5.91)	0.155
Bicarbonate	24.12 ± 6.11	22.01 ± 4.71	0.92 (0.79-1.07)	0.355
pH	7.417 ± 0.05	7.374 ± 0.1	0.01 (0.01-74.88)	0.069
Echocardiographic features				
Recent AMI – n (%)	8 (25.8)	8 (16)	0.61 (0.22-1.73)	0.507
HF with previous heart disease – n (%)	22 (70.97)	40 (80)	1.83 (0.61-5.51)	0.429
History of HF and recent AMI – n (%)	1 (3.23)	2 (4)	-	0.999
Ejection fraction: % (± DP)	35.86 ± 10.79	36.09 ± 10.79	1.01 (0.97-1.05)	0.598
Left atrial diameter: mm (± DP)	39.51 ± 7.45	39.51 ± 7.45	1.02 (0.96 - 1.08)	0.624
Myocardial thickness – n (%)				
Increased	16 (51.61)	21 (42)	0.77 (0.31-1.90)	0.538
Normal	15 (48.39)	29 (58)	Reference	
LF systolic dysfunction – n (%)				
Mild	1 (3.23)	2 (4)	Reference	0.999
Moderate/severe	30 (96.77)	48 (96)	1.25 (0.18-2.31)	
Clinical outcomes – n (%)				
Death	3 (9.68)	16 (32)	1.21 (1.16-16.62)	**0.021**
Dialysis	0 (0)	3 (6)	–	0.437

AKI: acute kidney injury; OR: odds ratio;95% CI: 95% confidence interval; AMI: acute myocardial infarction; HF: heart failure; SAH: systemic arterial hypertension; DM: diabetes mellitus; CRD: chronic renal disease; AMI: acute myocardial infarction; LV: left ventricular; SD: standard deviation.

died during hospitalization, indicating an association of AKI with mortality (OR 1.21, 95% confidence interval [95% CI] between 1.16 and 16.62, p = 0.021). The need for dialysis was observed in only 6% of patients with AKI, but without statistically significant difference between the groups.

Deterioration of renal function was observed in 50 patients according to at least one diagnostic criteria (KDIGO and AKIN). Using the KDIGO criteria, kidney injury was detected in 61.7% of patients, whereas the AKIN was unable to detect AKI in 14% of patients (Table 3). However, in the present study, the KDIGO criteria was not superior to AKIN in detecting early changes in renal function. Multivariate analysis (Table 4) showed that AKI was an independent risk factor of mortality, with an adjusted OR of 8.187, 95%CI 1.402-17.190, and p=0.020.

Discussion

It is estimated that more than 85% of the world population live in low/medium income countries, where the development of scientific studies is typically low. Socioeconomic and environmental factors, including food shortage, affect the outcome of AKI in heart diseases and CRS, and such associations are frequently ignored in many studies.[6,7] The present study was conducted in a tertiary hospital, the main emergency referral center of a population of nearly one million people, in a state of low economic development (ranking 22nd of 27 federative units in terms of gross domestic product) in Brazil.[6,7,11]

However, in the study population, clinical and demographic features were similar to those reported in the literature, with a predominantly male, older patients, as reported by Spineti et al.,[3] where 58% of the sample were men, mean age of 63.5 ± 13 years. Liangos et al.[11] also shown a predominance of male, older patients, and DM, SAH, and CRD as the main comorbidities.

Studies on patients diagnosed with AKI have demonstrated that chronic conditions, especially DM and SAH, are more strongly associated with AKI.[11,12] However, similar to our study, Caetano et al.[13] did not find an association of CRS with a history of HF, DM, or elevated blood pressure at hospital admission, but with history of kidney disease.

In a multicenter study, data of 105,388 patients with acutely decompensated HF were collected from 274 hospitals in the USA. The prevalence of CRS in this population was 30%, which was similar to that (32%) reported in the meta-analysis by Damman et al.[14] In our study, AKI was present in 61.7% of patients. This is condition, more and more common in HF patients, can be an aggravating factor for symptom severity, and change not only the clinical course of disease, but also response to treatment.[15] In some studies, preexisting CRD in patients admitted for decompensated HF was associated with development of AKI in all cases.[16]

Analyses of laboratory data of patients admitted with acute CRS had higher values of urea, creatinine and potassium compared with those without renal injury.[3,13] Other studies not only corroborated these findings, but also showed that small changes in creatinine levels are significantly associated with an increase in mortality in patients with AKI.[17]

In the present study, most patients admitted for decompensated HF had a history of heart disease, and this factor was not associated with the development of AKI. Regarding the echocardiographic parameters, including left ventricular ejection fraction (LVEF), no cardiac structural

Table 3 – Incidence and staging of acute kidney injury according to the diagnostic criteria proposed by the Acute Kidney Injury Network (AKIN) and the Kidney Disease: Improving Global Outcomes (KDIGO) in patients with cardiorenal syndrome

AKI staging	AKIN		KDIGO		p – value
	N	%	N	%	
Stage 1	35	43.21	39	48.15	0.642
Stage 2	3	3.7	5	6.17	0.479
Stage 3	5	6.17	6	7.41	0.763

AKI: acute kidney injury.

Table 4 – Multivariate analysis of variables related to cardiorenal syndrome in hospitalized patients with decompensated heart failure or recent acute myocardial infarction (n=81)

Variables	Adjusted OR (95%CI)	p
Male sex	0.796 (0.241-2.632)	0.708
Age (+ 1 year)	1.010 (0.967-1.055)	0.651
Systemic arterial hypertension	2.228 (0.684-7.261)	0.184
Chronic renal disease	6.622 (0.901-48.693)	0.063
Urea (+1 mg/dL)	1.005 (0.983-1.028)	0.660
Acute kidney injury	8.187 (1.402-17.190)	0.020

OR: Odds ratio;95%CI: 95% confidence interval.

or functional parameter was associated with the course of CRS. Although AKI is equally prevalent in HF due to systolic dysfunction and diastolic dysfunction, kidney injury is generally more severe in patients with reduced LVEF as compared with those with normal LVEF, and found in more than 70% of patients admitted with cardiogenic shock.[2] Similar findings were reported in another study that showed that 86% of patients with AKI had HF and LVEF<40%.[3]

Caetano et al.,[13] in an echocardiographic study of patients with CRS, showed that 48.4% of patients had preserved systolic function (LVEF ≥ 50%). Among the patients with AKI, 26 (56.6%) had compromised ejection fraction, whereas 47 (43.1%) of patients without AKI had acute renal dysfunction. In the same study,[13] moderate or severe mitral insufficiency was found in 68.4% and 45.1% of patients with and without AKI, respectively (p=0.014). In addition, mean LVEF was approximately 36% and only three patients had a LVEF > 50%, with no difference between patients with and without AKI.

Studies have reported the occurrence of AKI in HF in patients with both reduced and preserved LVEF,[2,3,13] which reinforces the need for evaluating the cardiac and hemodynamic function in patients with worsening renal function. Studies by Mullens et al.[18] and Damman et al.[19] evaluated the hemodynamic profile of patients with cardiovascular disease using invasive methods and intensive therapies. Thus, it is suggested that other parameters, indicative of renal injury, such as changes in the vena cava, could be evaluated by echocardiography, a non-invasive method, since these same studies have reported a correlation between increased central venous pressure and worsening of renal function. Although the assessment of inferior vena cava diameter during inspiration and expiration is possible by echocardiography, few studies have investigated these parameters.

Need for dialysis was seen in 6% of our patients, which is in accordance with the study by Li et al.,[20] with a cohort of 1,005 Chinese patients (6.4%). Also, the meta-analysis by Vandenberghe et al.[5] showed a need for renal replacement therapy in 4.6% of patients with CRS due to decompensated HF and 2.3% of patients with CRS due to other causes. According to Forman et al.,[21] in HF patients with longer hospitalizations and in-hospital death, complications are more common in patients with AKI. In our study, we observed a 32% mortality rate in patients with AKI, which represented an independent risk factor for mortality (OR 8.187 [1.402 – 17.190], p=0.020). Hata et al.,[22] in a retrospective analysis of 376 patients admitted to the intensive care unit (ICU) with decompensated HF, AKI was detected in 73% of patients and was correlated with high in-hospital mortality (10.5% versus 1.0% in non-AKI patients; p<0.01), and longer hospital stay as compared with the control group. In our study, CRS alone was not considered a risk factor by the multivariate analysis (OR 6.622 [0.901-48.693], p=0.063), possibly because of the small sample size. However, Damman et al.[14] reported in a meta-analysis, a significant association between CRS and mortality (2.3 [2.20-2.50], p < 0.001). In another study, higher in-hospital mortality was found in patients with AKI, especially among those who had greater worsening of renal function. Of 18 patients who died, 17 (94.5%) had AKI, 76.5% AKIN stage 3 and 23.5% AKIN stage 2.[16]

Barros et al.,[16] in a study with 85 hospitalized patients admitted to the ICU with decompensated HF, found that 76,5% of patients had AKI, mainly at stage 3 (38.8%) (AKIN criteria), followed by stage 2 (32.9%) and stage 1 (4.7%). We should consider that, in general, critically ill patients in ICUs have impairment of many organs, including renal dysfunction. Therefore, it is possible that patients with AKI at more advanced stages may be found in this population.

According to a comparative study between RIFLE (Risk, Injury, Failure, Loss and End-Stage Kidney, classification proposed by the Acute Dialysis Quality Initiative group), AKIN and KDIGO in patients in the post-operative period of cardiac surgery, the prognostic power of the KDIGO criteria was superior to both AKIN and RIFLE.[23] In our study, however, KDIGO was not superior to AKIN, which was similar to the findings reported by Roy et al.,[24] who evaluated 637 patients and found a similar performance of AKIN, KDIGO and RIFLE. In a large Chinese retrospective, cohort study, that included patients with HF, Li et al.[20] showed that KDIGO was superior to both AKIN and RIFLE, but the proportions of patients with AKI at stages 2 and 3 were higher than in our study.

Limitations

This study has some limitations that need to be considered. First, this was a single-center study, involving a small number of patients. Second, there were limitations inherent to the retrospective design of the study, including reliance on medical records. Although all specific requirements for modeling and variable selection of logistic regression were met, the possibility that other variables influenced the results cannot be excluded. Likewise, creatinine measurements were not recorded daily, which may have affected the evaluation of AKI staging. Finally, the small number of patients with AKI at initial stages may have influenced the performance of the AKIN and KDIGO diagnostic criteria.

Conclusion

In this population of patients admitted to a public tertiary hospital of a low-income region, with decompensated HF and a history of heart disease or recent AMI, there was a high occurrence of AKI, which was an independent risk factor for mortality. CRS was a risk factor for AKI. In addition, cardiac structural and functional changes, evaluated by echocardiography, were not associated with the development of AKI. The KDIGO and AKIN diagnostic criteria showed similar performance in this population.

Author Contributions

Conception and design of the research: Nascimento GVR;Acquisition of data and Statistical analysis: Nascimento GVR, Brito HCD;Analysis and interpretation of the data and Writing of the manuscript: Nascimento GVR, Brito HCD, Lima CEB;Critical revision of the manuscript for intellectual contente: Nascimento GVR, Lima CEB.

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. Rangaswami J, Chair V, Bhalla V,Chang TI, Costa S, Lentine KL, et al. Cardiorenal syndrome: classification, pathophysiology, diagnosis and treatment strategies. A scientific statement from the American Heart Association. Circulation. 2019; 139(16): e840-e78.
2. Ronco C, Haapio M, House AA,Anavekar NS, Bellomo R. Cardiorenal syndrome. J Am Coll Cardiol. 2008; 52(19): 1.527-39.
3. Spineti PPM, Tedeschi B, Sales ALF. Incidência e preditores de síndrome cardiorrenal aguda durante tratamento de insuficiência cardíaca descompensada: análise de 332 hospitalizações consecutivas. Rev Socerj. 2009; 22(2): 93-8.
4. Kellum JA, Lameire N, Aspelin P, Barsoum RS, Burdman EA, Goldstein SL, et al. Kidney disease: improving global outcomes (KDIGO) acute kidney injury work group. KDIGO clinical practice guideline for acute kidney injury. Kidney Inter Suppl. 2012; 2: 1-138.
5. Vandenberghe W, Gevaert S, Kellum JA et al. Acute kidney injury in cardiorenal syndrome type 1 patients: a systematic review and metanalysis. Cardiorenal Med. 2016; 6(2): 116-28.
6. Nascimento GVR, Silva MN, Carvalho Neto JD, Bagshaw SM, Peperstraete H, Herck I, et al. Outcomes in acute kidney injury in noncritically ill patients lately referred to nephrologist in a developing country: a comparison of AKIN and KDIGO criteria. BMC Nephrol. 2020; 21(1), 94.
7. Banerjee S, Radak T. Association between food insecurity, cardiorenal syndrome and all-cause mortality among low-income adults. Nutrit Health. 2019; 25(4), 245-52.
8. Bagshaw SM, George C, Bellomo R. A comparison of the RIFLE and AKIN criteria for acute kidney injury in critically ill patients. Nephrol Dial Transplant. 2008; 23: 1.569-74.
9. Mehta RL, Kellum JA, Shah SV et al. Acute kidney injury network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007; 11(2): R31.
10. Instituto Brasileiro de Geografia e Estatistica – IBGE. Produto interno bruto – PIB. Disponível em: https://www.ibge.gov.br/explica/pib.php. Acesso em: 13 maio 2020.
11. Liangos O, Wald R, O' Bell JW et al. Epidemiology and outcomes of acute renal failure in hospitalized patients: a national survey. Clin J Am Soc Nephrol. 2006; 1(1): 43-51.
12. Bucuvic EM, Ponce D, Balbi AL. Fatores de risco para mortalidade na lesão renal aguda. Rev. Assoc. Med. Bras. 2011; 57(2): 158-63.
13. Caetano F, Barra S, Faustino A, Botelho A, Mota P, Costa M et al. Cardiorenal syndrome in acute heart failure: a vicious cycle? Rev Port Cardiol. 2014; 33(3): 139-46.
14. Damman K, Valente MA, Voors AA, O'Connor CM, Velalhuisen DJ, et al. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. Eur Heart J; 35(7): 455-69.
15. Adams KF Jr, Fonarow GC, Emerman C,L,ejentel T, Costanzo MR, Abraham WT et al. Characteristics and outcomes of patients hospitalized for heart failure in the United States: rationale, design, and preliminary observations from the first 100,000 cases in the Acute Decompensated Heart Failure National Registry (ADHERE). Am Heart J. 2005; 149(2): 209-16.
16. Barros LCN, Silveira FS, Silveira MS, Morais TC. Acute kidney injury in hospitalized patients with decompensated heart failure. J Bras Nefrol. 2012; 34(2): 122-9.
17. Chertow GM, Burdick E, Honour M, Bonsentre V, Bates DW. et al. Acute kidney injury, mortality, length of stay and costs in hospitalized patients. J Am Soc Nephrol. 2005; 16(11): 3.365-70.
18. Mullens W, Abrahams Z, Francis GS, Sokos G, Taylor DO, Starling RC, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. J Am Coll Cardiol 2009; 53(7): 589-96.
19. Damman K, Deursen VM, Navis G, Voors AA, Veldhuisen D, Hellege HC. Increased central venous pressure is associated with impaired renal function and mortality in a broad spectrum of patients with cardiovascular disease. J Am Coll Cardiol. 2009; 53(7): 582-8.
20. Li Z L, Cai L, Liang X,Du Z, Chen Y, An S, et al. Identification and predicting short-term prognosis of early cardiorenal syndrome type 1: KDIGO is superior to RIFLE or AKIN. PLoS One. 2014; 9(12): e114369.
21. Forman DE, Butler J, Wang Y,Abraham WT, O'Connor CM, Gottlieb S, et al. Incidence, predictors at admission and impact of worsening renal function among patients hospitalized with heart failure. J Am Coll Cardiol. 2004; 43(1): 61-7.
22. Hata N, Yokoyama S, Shinada T, Koboyashi N, Shirakabe A, Tomita K, et al. Acute kidney injury and outcomes in acute decompensated heart failure: evaluation of the RIFLE criteria in an acutely ill heart failure population. Eur J Heart Fail. 2010; 12(1): 32-7.

Assessment of Renal Function in Patients with Heart Failure

Alfredo Jose Mansur[1] *and Victor Sarli Issa*[2]

Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo,[1] *São Paulo, SP - Brazil*
University Hospital Antwerp,[2] *Edegem, Antwerp - Belgium*

Short Editorial related to the article: Type 1 Cardiorenal Syndrome in Decompensated Heart Failure Patients in a Low-Income Region in Brazil: Incidence of Acute Kidney Injury (AKIN and KDIGO Criteria), Need for Dialysis and Mortality

Heart failure is a systemic condition that may lead to impairment of many organ systems and physiological functions that may cause symptoms and may have a negative influence in the prognosis of the patients.[1,2] Compromising renal function may be one of the ailments of patients with heart failure.[2,3]

Prevention, diagnosis and treatment of this complication are key issues in patient care; strategies of categorization of acute renal lesions have been developed and are helpful in clinical practice.[1]

A first step would be to study local experience to estimate its frequency, clinical characteristics and evaluation of severity. Causes of acute kidney injury were recognized to vary by country and economic status.[4] This important step was provided in a retrospective study based on hospital charts of a referral hospital in a Brazilian northeast state capital to address the comparison of two methods of evaluating renal dysfunction.[5]

They studied[5] a sample of 81 patients admitted to the Hospital, diagnosed with heart failure (16 of them with recent myocardial infarction), mean age 67 years, men (53%) and women (47%). Acute kidney injury was diagnosed in 50/81 patients; mortality was 16/50 (32%) in patients with acute kidney injury and 3/31 (9,68%) in patients without acute kidney injury. Dialysis was performed in three patients with acute kidney injury. The authors found that the KDIGO score (Kidney Disease: Improving Global Outcomes) indicated renal injury in 61,7% of the cases; the AKIN (Acute Kidney Injury Network) criteria did not indicate acute renal lesion in 14% of the patients. The authors concluded that a relationship between the cardiac conditions in this study sample did not demonstrate a clear relationship with acute kidney lesions; the scores did not demonstrate a significant difference in performance for guidance in the diagnosis of acute kidney lesions.

Prevention is a key step in patient care. Prevention of acute kidney injury may be part of the care of patients with heart failure and include: control of contributing factors to the occurrence and development of both renal and cardiac dysfunctions (such as diabetes mellitus and arterial hypertension); prevention and control of factors aggravating kidney function such as hypovolemia, hypotension and use of nephrotoxic agents; prevention and control of factors aggravating heart function such as hypo- and hypervolemia, acute blood pressure abnormalities, ischemia and use of drugs that could impair the heart function, and others; appropriate treatment of heart failure with disease-modifying therapies and, ideally, use of therapies that could positively impact the renal function.

In the event of established acute kidney injury, early diagnosis or prompt diagnosis may be crucial and the use of appropriate diagnostic criteria play a central role. One of the most used markers in medical practice is serum creatinine and elevation equal to or greater than 0.3 mg/dl has been associated with increased risk of hospital death and prolonged hospitalization. However, the non-linear relationship between creatinine and glomerular filtration rate and the influence of factors such as metabolic status, age, gender, race, and nutritional status limit an accurate application in clinical practice.[6]

A way to compensate for these limitations was the development of equations for calculating glomerular filtrating rate using variables such as sex, age, race, and body surface area. The most commonly used equations are Cockcroft-Gault, MDRD (Modification of Diet in Renal Disease) and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). Despite being more accurate, they also face limitations in special populations such as elderly, underweight, obese and diabetic patients.

Scores frequently used in clinical practice use either creatinine (AKIN), glomerular function estimates (KDIGO) or a combination of both (RIFLE), in association with other data, such as albuminuria. Other markers of renal function including kidney injury molecule 1 (KIM1), isoform 1, N-acetyl-β-D-glycosaminidase (NAG), interleukin 18, cystatin C, neutrophil gelatinase-associated lipocalin (NGAL), and urinary exosomes are currently under investigation.[7]

Keywords

Heart Failure/complications; Kidney Diseases/complications; Prognosis; Prevention and Control; Risk Factors; Hypertension; Diabetes Mellitus; Hypovolemia.

Mailing Address: Alfredo Jose Mansur •
Instituto do Coração, Faculdade de Medicina da Universidade de São Paulo - Cardiologia Clínica, Ambulatórios Gerais - Av. Dr. Enéas de Carvalho Aguiar, 44. Postal Code 05403-000, São Paulo, SP – Brazil
E-mail: ajmansur@cardiol.br, ajmansur@incor.usp.br

DOI: https://doi.org/10.36660/abc.20210467

References

1. Thomas ME, Blaine C, Dawnay A, Devonald MA, Ftouh S, Laing C, et al. The definition of acute kidney injury and its use in practice. Kidney Int. 2015 Jan;87(1):62-73. doi: 10.1038/ki.2014.328.
2. Villacorta H, Villacorta AS, Villacorta LSC, Xavier AR, Kanaan S, Rohen FM,et al. Worsening Renal Function and Congestion in Patients with Acute Heart Failure: A Study with Bioelectrical Impedance Vector Analysis (BIVA) and Neutrophil Gelatinase-Associated Lipocalin (NGAL). Arq Bras Cardiol. 2021 Apr;116(4):715-24.
3. Leite AM, Gomes BFO, Marques AC, Petriz JLF, Albuquerque DC, Spineti PPM, et al. Acute Cardiorenal Syndrome: Which Diagnostic Criterion to Use And What is its Importance for Prognosis? Arq Bras Cardiol. 2020 Jul;115(1):127-33.
4. Mehta RL, Burdmann EA, Cerdá J, Feehally J, Finkelstein F, García-García G, et al. Recognition and management of acute kidney injury in the International Society of Nephrology 0by25 Global Snapshot: a multinational cross-sectional study. Lancet. 2016 May 14;387(10032):2017-25. doi: 10.1016/S0140-6736(16)30240-9. Erratum in: Lancet. 2016 May 14;387(10032):1998.
5. Nascimento GVR, Brito HCD, Lima CEB. Type 1 Cardiorenal Syndrome in Decompensated Heart Failure Patients in a Low-Income Region in Brazil: Incidence of Acute Kidney Injury (AKIN and KDIGO Criteria), Need for Dialysis and Mortality. Arq Bras Cardiol. 2021; 117(2):385-391. doi: https://doi.org/10.36660/abc.20200097.
6. Blair JE, Pang PS, Schrier RW, Metra M, Traver B, Cook T, et al. EVEREST Investigators. Changes in renal function during hospitalization and soon after discharge in patients admitted for worsening heart failure in the placebo group of the EVEREST trial. Eur Heart J. 2011 Oct;32(20):2563-72. doi: 10.1093/eurheartj/ehr238.
7. Lassus JP, Nieminen MS, Peuhkurinen K, Pulkki K, Siirilä-Waris K, Sund R,et al. FINN-AKVA study group. Markers of renal function and acute kidney injury in acute heart failure: definitions and impact on outcomes of the cardiorenal syndrome. Eur Heart J. 2010 Nov;31(22):2791-8. doi: 10.1093/eurheartj/ehq293.

Peculiar Aspects of Patients with Inherited Arrhythmias during the COVID-19 Pandemic

Luciana Sacilotto,[1] Natalia Quintella Sangiorgi Olivetti,[1] Cristiano Faria Pisani,[1] Tan Chen Wu,[1] Ludhmila Abrahão Hajjar,[1] Sissy Lara de Melo,[1] Sávia Christina Pereira Bueno,[1] Esteban Wisnivesky Rocca Rivarola,[1] Muhieddine Omar Chokr,[1] Carina Abigail Hardy,[1] Denise Tessariol Hachul,[1] Francisco Carlos da Costa Darrieux,[1] Mauricio Ibrahim Scanavacca[1]

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

Abstract

Since December 2019 we have observed the rapid advance of the severe acute respiratory syndrome caused by the new coronavirus (SARS-CoV-2). The impact of the clinical course of a respiratory infection is little known in patients with hereditary arrhythmias, due to the low prevalence of these diseases. Patients who present with infectious conditions may exacerbate hidden or well-controlled primary arrhythmias, due to several factors, such as fever, electrolyte disturbances, drug interactions, adrenergic stress and, eventually, the septic patient's own myocardial damage. The aim of this review is to highlight the main challenges we may encounter during the Covid 19 pandemic, specifically in patients with hereditary arrhythmias, with emphasis on the congenital long QT syndrome (LQTS), Brugada syndrome (SBr), ventricular tachycardia polymorphic catecholaminergic (CPVT) and arrhythmogenic right ventricular cardiomyopathy.

Since December 2019 we have observed the rapid advance of the severe acute respiratory syndrome caused by the new coronavirus (SARS-CoV-2), the first cases of which arose in Wuhan, China, subsequently arriving in Brazil. Retrospective studies have shown that old age was an independent predictor of mortality by COVID-19. Other risk factors impacting mortality were systemic arterial hypertension, chronic pulmonary obstructive disease, immunosuppression, type-2 diabetes mellitus, obesity, and severe cardiopathy (heart failure, coronary disease, or cardiomyopathies).[1,2]

Overall, complications due to arrhythmias in patients with pneumonia, particularly atrial fibrillation, are relatively common.[3,4] Cardiac arrest occurs in about 3% of hospitalized patients;[5] however, less than 20% of cardiac rhythms of in-hospital events are reported as being electrically reversible to sinus rhythm (by cardioversion or defibrillation), i.e., ventricular tachycardia/fibrillation (VT/VF).[6] In such patients, the primary arrhythmogenic mechanism is myocardial injury due to ischemia or inflammation.[4]

Keywords

COVID-19; Aarrhythmogenic Right Ventricular Cardiomyopathy; Brugada Syndrome; Long QT Syndrome; Catecholaminergic Polymorphic Ventricular Tachycardia.

Mailing Address: Maurício Ibrahim Scanavacca •
Instituto do Coração - Unidade de Arritmia – Av. Dr. Enéas de Carvalho Aguiar, 44. Postal Code 01421-001, São Paulo, SP – Brazil
E-mail: mauricio.scanavacca@incor.usp.br
Manuscript received May 05, 2020, revised manuscript November 11, 2020, accepted November 25, 2020

DOI: https://doi.org/10.36660/abc.20200391

The impact of a clinical evolution to sepsis, or specifically of the respiratory infections, is poorly known in patients who harbor inherited arrhythmias, due to the low prevalence of these diseases.[7] Moreover, most inherited arrhythmias generally have incomplete penetrance and are age-dependent,[8] being mainly expressed in young patients who, in turn, have a lower risk of developing severe infectious conditions.

Patients presenting with more severe infectious conditions may have exacerbation of concealed or well-controlled arrhythmias, due to several factors such as fever, electrolytic disorders, drug interaction, adrenergic stress and, eventually, the septic patient's own myocardial injury. All these factors may alter the ion channels balance, rendering these patients with inherited arrhythmias potentially more vulnerable.

Lethal events in patients with inherited arrhythmias may be triggered by physical and emotional stress. The psychosocial impacts of the pandemic, which correlate to depression, stress, anxiety and panic syndrome, further aggravated by social isolation and the confrontation of fear and grief, may all predispose to a higher occurrence of arrhythmias.[9] The possible need for a temporary suspension of medications (β−blockers and antiarrhythmic drugs) in hemodynamically unstable patients, the use of vasopressor drugs with catecholaminergic effects, and hydro-electrolytic disorders may be linked to a higher risk for potentially fatal events. Therefore, the pandemic period itself is a warning for the need to warrant vigilance and orientation directed to these patients who, once harboring rare diseases, are not well represented in clinical studies. In case of infection by SARS-COV2, there is not enough epidemiological data on this population to categorize them as a risk group, thus generating insecurity for both physician and patient. In Table 1 we rank the in- and out-of-hospital general healthcare measures that should be adopted for patients with previously known genetic arrhythmias.

For all the aforementioned reasons, it is important to review the main challenges faced during the COVID-19 pandemic,[7] specifically in this subpopulation, highlighting congenital long-QT syndrome (LQTS), Brugada syndrome (BrS), catecholaminergic polymorphic ventricular tachycardia (CPVT), and arrhythmogenic right ventricular cardiomyopathy (ARVC).

Congenital Long-QT Syndrome

Overview

LQTS affects 1:2,000 individuals and is characterized by prolongation of the QT interval on the standard 12-lead ECG and a propensity for syncope or seizures secondary to *torsades de pointes* (TdP) and sudden cardiac death (SDC).[10]

Table 1 – Out-of-hospital and inpatient care during COVID-19 pandemic in patients with inherited arrhythmias

Out-of-hospital care
• Avoid emotional stress
• Practice good hygiene and physical distancing
• Check for the risk of social distancing
• Keep beta-blockers and antiarrhythmic drus, as appropriate
• Attention with alarm symptoms (syncope, presyncope and palpitations) and optimal pharmacological treatment and adherence to medication
Out-of-hospital and inpatient care
• Keep euthermia – fever should be treated early, especially in patients with LQTS2 and BrS
• Azithromycin and Hydroxychloroquine/Chloroquine must be discouraged in patients with LQTS
• Avoid the association of hydroxychloroquine with amiodarone or sotalol due to the risk of TdP
• The drugs that may lengthen the QT interval is available on www.credibledrugs.org
• Drugs interactions are available on www.online.epocrates.com
• Be aware of QT control protocols of each hospital

LQTS: Long QT syndrome, BrS: Brugada Syndrome, ARVC: arrhythmogenic right ventricle cardiomyopathy; TdP: Torsades de pointes.

LQTS is associated to defects that either increase the sodium and calcium (respectively Ina and Ica L) depolarization currents, or attenuate the potassium (IKs, IKr and IK1) repolarization currents, leading to a prolonged cardiac action potential that results in QT-interval prolongation.[11] Clinical peculiarities and molecular diagnosis allow for LQTS classification into subtypes, mainly LQTS-1 (IKs channel, gene *KCNQ1*), LQTS-2 (hERG or IKr channels, gene *KCNH2*), or LQTS-3 (Ina channel, gene *SCN5A*).

The QT interval must be preferably measured from leads DII or V5 (Figure 1) and corrected by the preceding RR interval using Bazett's formula, ideally at a 60 to 80 bpm heart rate.[12] The present guidelines define that QTc is prolonged when its value is above 450 ms in men and 460 ms in women. However, 5% to 10% of healthy individuals have a QTc > 460 ms; therefore, other clinical data are necessary to establish LQTS diagnosis. For these cases, the use of Schwartz score is recommended.[13,14] There is greater specificity for LQTS only when QTc values are above 480 ms in the absence of secondary causes.[14] On the other hand, about 30% of the patients have the concealed form of LQTS, represented by genetic background and normal QT interval, so the family history and a genetic test are relevant in case of clinical suspicion in these patients.

The standard treatment for patients with LQTS is β-adrenergic blockade using nadolol/propranolol, in addition to avoiding drugs that prolong the QT interval. The indication for left cardiac sympathetic denervation and ICD remains restricted to cases with greater risk for potentially fatal arrhythmic events.[14]

Healthcare during the COVID-19 pandemic

Cardiac ion channels are modulated by the autonomic nervous system, since the cardiac repolarization time is constantly adjusted by the heart rate. In a context of adrenergic stress, there is an increase in heart rate, with potassium channel phosphorylation and increased opening velocity in normal conditions. In situations of genetically-determined protein defect, this adjustment is impaired, thus slowing channel inactivation and allowing for an imbalanced entrance of calcium and occurrence of early after-depolarization (EAD). While the heart rate remains high, there may be some inhibition of these triggers; however, when the metabolic situation leads to bradycardia or RR interval irregularity, there is an increased repolarization dispersion and greater occurrence of EAD. Depending on the cell excitability threshold, EAD gives rise to ventricular extrasystoles (or "premature ventricular beats - PVBs"), TdP/VF.[11]

The suspension or reduction of the chronic use of β−blockers for the treatment of LQTS may aggravate the occurrence of potentially fatal arrhythmias; therefore, there should be a strict maintenance of medications for patients treated at home, while in critically-ill patients, the decision must be guided by their hemodynamic stability.

Ion current balance depends on the cell level of those ions, which can be dynamic in critically-ill patients. Hypokalemia, hypocalcemia and hypomagnesemia lead to the emergence of EAD, increased dispersion of repolarization, and TdP occurs more easily in LQTS carriers. Keeping potassium levels between 4.5 and 5 mg/dL might be a protective strategy.[7]

Sepsis or septic shock are situations associated with high adrenergic tone due to pain/discomfort, in addition to the inflammatory condition itself. LQTS-1 and LQTS-2 carriers are those who present with arrhythmias triggered mainly by adrenergic stress, being therefore more prone to such critical situations. The presence of fever may influence the biophysical properties of temperature-sensitive channels, particularly the hERG channels affected in LQTS-2.[15] Contrarywise, hypothermia is also associated with prolongation of the QT interval, albeit with a low risk of TdP induction.[16]

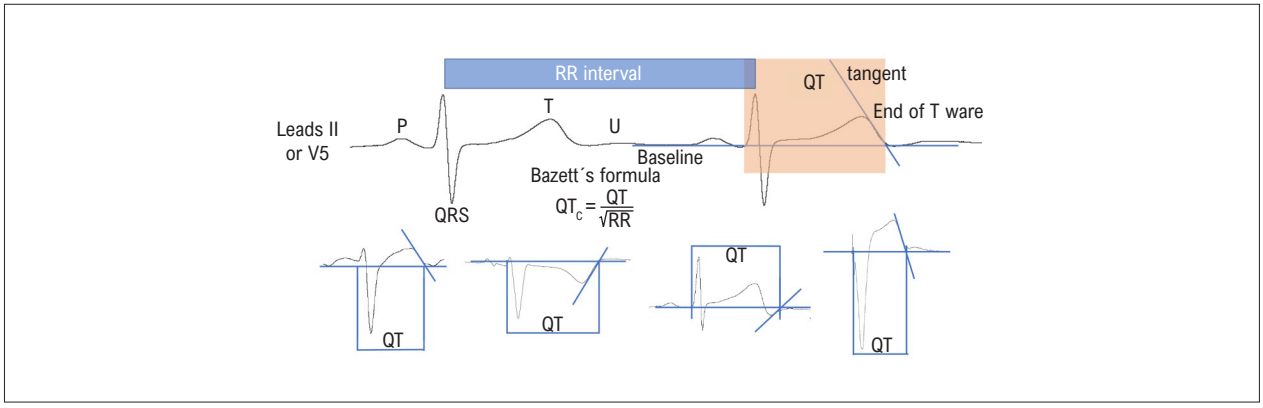


Figure 1 – *QT interval measurement in a patient with Long QT Syndrome. Source: InCor-HCFMUSP collection.*

Myocardial inflammatory injuries change the cell membrane potential, generating repolarization dispersion and susceptibility to ventricular arrhythmias.[17] Furthermore, cytokines and antibodies may link to the cardiac ion channels and lead to inflammation-induced channelopathy, presumably with greater severity in LQTS patients.[18]

Potassium-channel (hERG) blocking drugs may further prolong the cardiac repolarization, thus increasing the risk for fatal arrhythmias. The indication of these medications must be strictly weighed, especially in out-of-hospital regimens that lack continuous monitoring. In addition, drugs that lead to P450 3A4 (CYP3A4) cytochrome inhibition may further increase the serum level of drugs that prolong the QT interval.[7]

There is a list of drugs in www.crediblemeds.org that includes chloroquine/hydroxychloroquine and azithromycin. In critically-ill patients, other drugs that pose risk are often administered, such as antiemetic (ondansetron and metoclopramide),[19] antipsychotic (haloperidol), vasoactive (noradrenaline, dobutamine), analgesic (tramadol), and sedative drugs (etomidate, propofol).[20]

The use of chloroquine and hydroxychloroquine, associated or not to azithromycin, is controversial in COVID-19 patients, of which efficacy has been demonstrated *in vitro*,[21] but still lacking support from clinical studies. In a recent publication, Mazzanti et al. suggested that a cumulative 2g dose of hydroxychloroquine in 5 days, as it is adopted in 30% of all ongoing studies of hydroxychloroquine (www.clinicaltrials.gov), leads to mild prolongation of the QTc interval in patients with normal baseline QTc (average increase of 20 ms), without increasing the risk for life-threatening arrhythmic complications.[22] In another series of patients with systemic lupus erythematosus, with mean QTc interval of 443 ± 25.3 ms (373 – 518 ms), QTc interval prolongation occurred in 14.2% of patients using chloroquine.[23] Considering that LQTS patients already are more prone to TdP-type pro-arrhythmias, the use of chloroquine or hydroxychloroquine, mainly in association with azithromycin, must be discouraged in patients with LQTS.[12]

Polypharmacy is an issue requiring multidisciplinary caution on the part of both physicians and pharmacists; in LQTS patients, this becomes an even more relevant concern, due to the risk of imminent sudden death when they are exposed to such drugs. Specifically in these patients, one must promptly discuss the risks and benefits of each medication.

In case of TdP occurrence degenerating into VF, defibrillation and cardiopulmonary resuscitation are required. TdP usually has a self-limited presentation with spontaneous resolution; however, prevention of TdP recurrence is the most challenging factor. Emergency measures include minimizing pro-arrhythmic medications and suppressing factors that give origin to early after-potentials.[24]

The primary measure aimed to suppress EAD in LQTS is to avoid bradycardia and pause episodes. In patients with acquired LQTS it is possible to try pharmacological measures, such as intravenous isoprenaline; on the other hand, in patients with congenital LQTS, overdriving should only be done by atrial or ventricular stimulation, with a temporary (transcutaneous or transvenous) pacemaker implantation. The administration of 2g followed by continuous infusion (3 to 10mg/min) of magnesium sulphate is an adjunct therapy in both circumstances, aiming to reduce the oscillation amplitude at phase 3 of the membrane action potential. In case of refractoriness, sedation may be necessary to cease the adrenergic stimulus.[25]

Brugada Syndrome

Overview

BrS affects about 1 in 5,000 people, with a male gender predominance. The BrS diagnosis is established by the ECG, through the presence of ST-segment elevation >2mm in at least one right precordial lead (V1-V2), in standard (fourth intercostal space, ICS) or superior ICS (second or third ICS), (Figure 2) followed by a negative T-wave (type-1 pattern). The main diagnostic and classification challenge is the fact that this is a dynamic ECG pattern in most patients,[14] therefore it may be spontaneously documented or obtained after a provocative test using specific drugs (e.g., ajmaline).

In the absence of secondary causes, the presence of a spontaneous BrS type-1 ECG pattern is sufficient for the diagnosis. In cases of BrS induced by fever or provocative tests, it would be necessary to add personal and familiar clinical data to precisely define the diagnosis. Recently, a scoring system (Shanghai score) was proposed for BrS, which may be used as a diagnostic tool.[26]

Secondary causes, the so-called BrS phenocopies, include the use of drugs that induce the elevation of the ST-segment (e.g. tricyclic drugs), electrolytic disorders, myocardial ischemia, and other forms of ST-segment distortion (presence of *pectus excavatum*) (Table 2).[27]

BrS genetics is more complex than the other primary electrical syndromes. *SCN5A*, the first identified gene, still remains a causative gene; however, all the other 20 genes reported in the recent literature lack a genotype-phenotype correlation.[28]

Therapy for BrS patients involves the avoidance of situations that facilitate the occurrence of potentially fatal arrhythmias (VT/VF), such as fever, use of illicit drugs, alcohol consumption, copious meals, or drugs that increase sodium channel blockade. Quinidine, an important I_{to} channel blocker, seems to be safe and able to reduce arrhythmic events in the clinical follow-up of high-risk patients.

The indication for ICD implantation is restricted to patients that have shown documented spontaneous sustained VT, aborted sudden cardiac death (aSCD), or as primary prevention for those presenting with a greater risk for arrhythmic events, like the presence of syncope. The electrophysiologic study (EPS) can be used for risk stratification of asymptomatic patients, with controversial results.[14] Radiofrequency ablation of the BrS substrate has emerged as an adjuvant therapy for recurrent ventricular arrhythmias and is being studied in patients without previous arrhythmic events.[29]

Healthcare in the COVID-19 pandemic

The first aspect to be considered in BrS patients is diagnostic accuracy, since this is a specific electrocardiographic pattern vulnerable to interpretation bias. The list of diseases that can mimic BrS ECG changes, the so-called phenocopies, must be carefully scrutinized for adequate guidance. (Table 2) It is possible to observe that many phenocopies may occur in an infectious condition, such as in myocarditis, electrolytic disorders, pulmonary thromboembolism and myocardial infarction.

Recording ECGs by placing the precordial leads at higher ICS, as depicted in Figure 3, increases the sensitivity for detecting Brugada-type ECG pattern, and may be preferred over the standard lead positioning in patients with suspected or confirmed diagnosis. It can be additionally performed in COVID-19 patients with a VT/VF cardiac arrest during ICU hospitalization, especially if associated with fever. On the other hand, for the analysis of common pathologies during the course of infection, such as myocarditis and infarction, placing precordial leads at higher ICS should be clearly identified in the ECG, to avoid misinterpretation related to R-wave progression, axis and QRS amplitude. QT interval measurement may be performed from D2 of the ECG with superior leads, since the peripheral leads are kept in standard position.

The main measures for the management of BrS patients in the ICU are the prevention of fever and the avoidance of certain medications that enhance channel defects (www.brugadadrugs.org). There are several examples of drugs that increase the risk of sudden death in BrS carriers, such as supportive drugs in hospitalized patients (diphenhydramine), drugs to treat arrhythmias (amiodarone and propafenone), anesthetic agents (propofol), and analgesic drugs (tramadol).

The importance of fever in patients with BrS is well established. Usually, there is an increase of the PR interval,

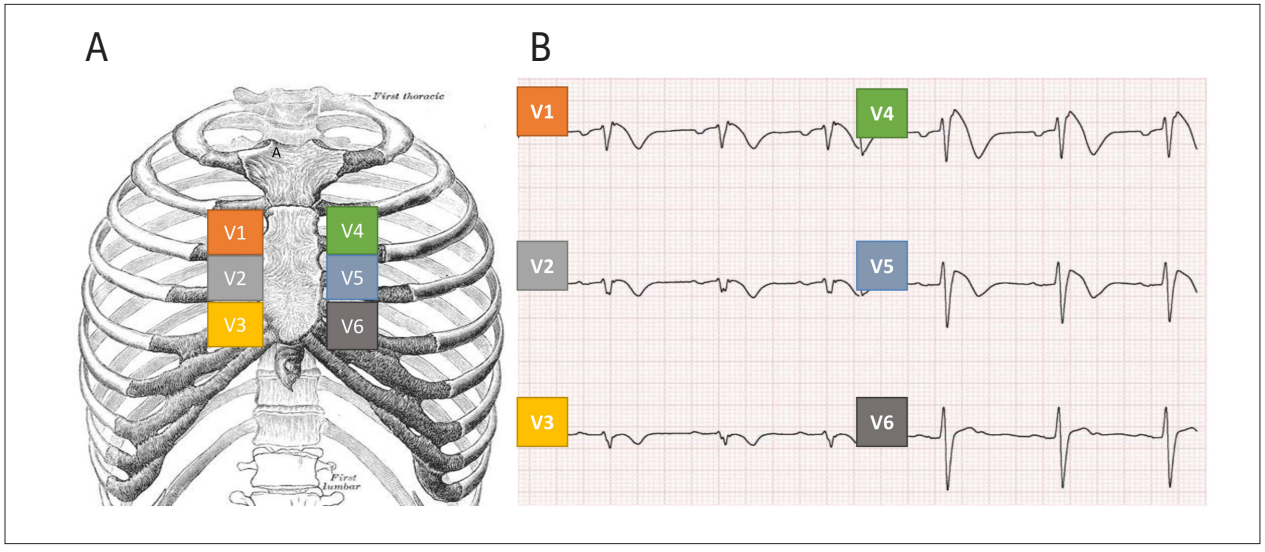


Figure 2 – *Placement of precordial leads in a patient with Brugada Syndrome. A) Precordial leads placed at superior intercostal space to increase the detection of Brugada type 1 pattern, as demonstrated in panel B. B) An asymptomatic 26-year-old girl, with a familiar history of sudden cardiac death. Source: InCor-HCFMUSP collection.*

QRS duration, and the J point. Fever also increases the risk of arrhythmia in people older than 70 years in whom the risk of the disease has already been reduced.[30] Those considered high-risk patients, with temperature over 38.5 ºC even after the administration of antipyretic drugs, should seek medical assistance.[7]

BrS was the first genetic arrhythmia to gain the spotlight in publications during the pandemic. The case of a patient who had the electrocardiographic BrS pattern unmasked by fever was reported. Because this was a young patient to whom the criteria for hospitalization would not apply, the authors chose to discharge him with *LifeVet*, which is not available in Brazil.[31]

Hydroxychloroquine and azithromycin may be indicated, depending on the evaluation of risks *versus* benefits. We suggest measuring serum electrolytes and considering continuous monitoring during the treatment. Prolongation of the QT interval and dispersion of repolarization with hydroxychloroquine and azithromycin might increase the risk for arrhythmia in patients with BrS, even without a direct relationship of these drugs with the depolarization channels.[23,32]

The management of electrical storm in BrS intends to increase the (depolarization) calcium channel to attain normalization of the ST segment elevation and the reduction of phase 2 reentries. Isoproterenol, as well as β-adrenergic agonists, can be effective, preferably in association with quinidine (unavailable in Brazil). The use of phosphodiesterase III inhibitors, such as oral cilostazol or intravenous milrinone, have shown a decrease in arrhythmogenicity in experimental models of BrS; however, studies on their effects in human beings are still under way.[33]

Arrhythmogenic Right and/or Left Ventricular Cardiomyopathy

Overview

The arrhythmogenic right and/or left ventricular cardiomyopathy (AR+/LVC), for a long time known as arrhythmogenic right ventricular dysplasia (ARVD), has an average prevalence of 1:5,000 among the general population.[34] This heterogeneous disease with various

Table 2 – Brugada Syndrome phenocopies

Metabolic conditions
Adrenal crisis, metabolic acidosis, hyperglycemia
Electrolyte disturbances
Hyperkalemia, hypokalemia and hyponatremia
Mechanical compression of right ventricle outflow tract
Tumors, pectus excavatum
Others
Myocardial ischemia and pulmonary embolism
Pericarditis and myocarditis
Exogenous Medications and Poisonings

Fonte: www.brugadadrugs.org[50]

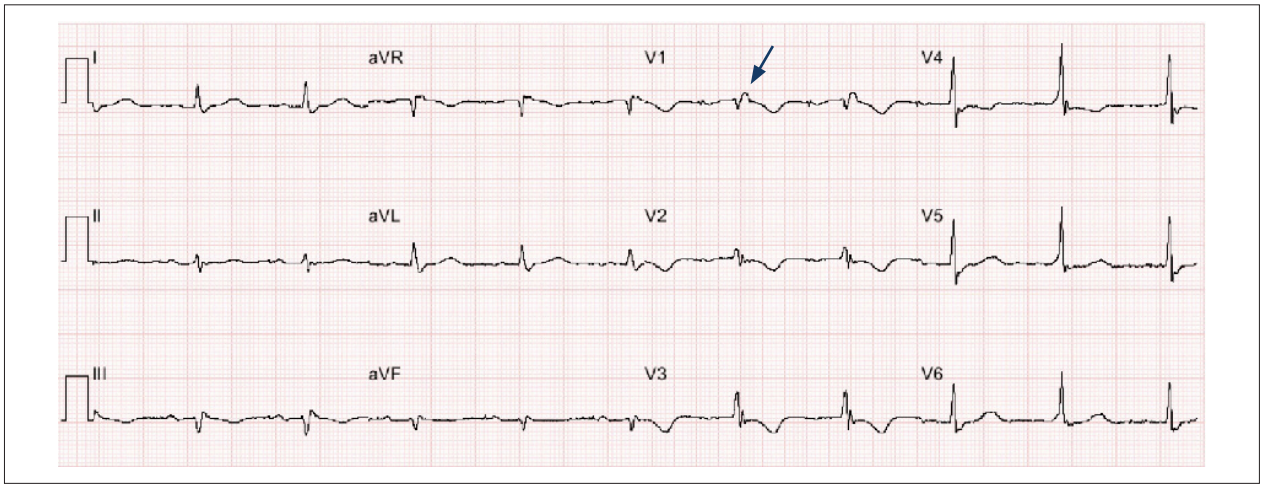


Figure 3 – *ECG of a patient with Arrhythmogenic right ventricle cardiomyopathy. A 45-year-old man recovered from sudden cardiac death. Presence of epsilon wave (arrow) and T wave inversion from V1 to V3, both major signals according to task force criteria. There is also low voltage QRS in limb leads, showing a severe ventricular impairment.*
Source: InCor-HCFMUSP collection.

clinical presentations can have sudden cardiac death as its first manifestation, occurring more often during physical exercise. There is no diagnostic standard gold test for AR+/LVC; there is a complex set of clinical tests that comprises the clinical history, electrocardiographic changes of depolarization and repolarization (Figure 3), cardiac imaging, anatomopathological and molecular evaluations.[35]

Currently, AR+/LVC is known to be a genetically-determined, mostly autosomal dominant condition, displaying some rare forms of autosomal recessive inheritance, such as in Naxos Disease[36] or Carvajal syndrome.[37] AR+/LVC penetrance is incomplete, the family is affected in up to 50% of the cases, and cases may still be underestimated due to the variant expression of the disease.

AR+/LVC clinical manifestation frequently emerges between the second and fourth decades of life.[38,39] The most common symptoms are palpitations, syncope, aSCD and congestive heart failure.

Mutations related to AR+/LVC typically affect genes encoding desmosomal proteins, which are important structures for cardiomyocyte cell adhesion, that play a key role in its physiopathology. Desmosomes, specialized structures of cell connection, are also important mediators acting in the intra- and inter-cell signal transduction.[40] Total loss of the complex desmosomal function leads to rupture of the cell-cell junction, detachment of myocytes and cell death. Fibro-fatty replacement of the cardiomyocytes contributes to the development of slow conduction areas that generate a scarred anatomic substrate for macro-reentry and ventricular arrhythmias. Fibrosis progresses from the epicardium to the endocardium, involving mainly the right ventricular free wall and causing its aneurysmatic thinning and dilation.[41]

The treatment is focused on the AR+/LVC clinical manifestation. There is no evidence that antiarrhythmic drugs prevent sudden death, and ICD is the indicated management for high-risk patients (aSCD and spontaneous VT). β−blockers are considered to be the first-line therapy for atrial arrhythmias, premature ventricular contractions (PVC), non-sustained VT, besides being important adjuvants for the control of appropriate or inappropriate ICD shocks (especially due to atrial arrhythmias). Sotalol, amiodarone and radiofrequency ablation may be therapeutic alternatives when β−blockers are either ineffective or poorly tolerated.[42]

Healthcare in the COVID-19 pandemic

Ventricular arrhythmias in AR+/LVC patients are often triggered by physical and emotional stress and have an important adrenergic-dependent component. Thus, the increased adrenergic release related to the compensatory response to the inflammatory syndrome accompanying the infectious condition may induce ventricular arrhythmias. β−blockers should be maintained for as long as the hemodynamic condition persists in these patients and, if possible, also the antiarrhythmic drugs (sotalol, amiodarone). Drugs with alpha- or beta-adrenergic effects, such as vasoactive amines (epinephrine, noradrenaline) and those with inotropic effects (dobutamine, milrinone) may increase the risk for ventricular arrhythmias; however, maintaining the hemodynamic stability is mandatory in critically-ill patients.

It is estimated that about 17% of patients hospitalized with COVID-19 need orotracheal intubation and mechanical ventilation for their recovery.[1] Mechanical ventilation has hemodynamic effects on the right ventricle, such as the increase of the right afterload and reduction of the right cardiac output in patients with right ventricular dysfunction and increased central venous pressure.[43]

The electrolytic disturbances (hypokalemia, hypocalcemia or hypomagnesemia) can also increase the susceptibility in patients with the anatomic substrate as it is the case in AR+/LVC; therefore, a thorough monitoring of electrolytes must be maintained.

Hydroxychloroquine and azithromycin are known to prolong ventricular repolarization. Thus, their association with class III Vaughan-Williams antiarrhythmics, such as sotalol and amiodarone, may enhance the risk for EAD-triggered activity and TdP/VF. An anti-viral effect of amiodarone has been proposed.[44] Antivirals such as ritonavir/lopinavir do not have the catecholaminergic effect of increasing the arrhythmic risk, and there is no evidence of drug-to-drug interaction with β−blockers / antiarrhythmic drugs in patients with AR+/LVC.[45]

Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT)

Overview

CPVT occurs in approximately 1 in 10.000 people, affecting mainly children in their first and second decades of life, with syncope or aSCD related to exercise or emotion. Resting ECG is within the normal parameters. Diagnosis is attained by performing a stress test, after ruling out cardiac structural disease, preferably by cardiac magnetic resonance imaging.

During the exercise test, premature ventricular beats arise with the increment of physical effort when the heart rate reaches 100 bpm, progressing to polymorphic VT and sometimes to the classic bidirectional VT, which is considered to be pathognomonic for this channelopathy (Figure 4).[10]

The arrhythmia implicated in CPVT occurs through the loss of calcium reuptake in the cytosol. Epinephrine release during exertion promotes an additional increase in calcium release in the sarcoplasmic reticulum during diastole. The triggering of the sodium and calcium currents leads to a sudden sodium inflow that can depolarize the cell and cause PVCs by delayed afterdepolarization. The emergence of random premature ventricular beats by the Purkinje system is responsible for the polymorphic aspect of the VT.

Approximately 60% of the patients with CPVT have a defective ryanodine cardiac receptor encoded by the RyR2 gene (CPVT type 1). CPVT type 2 is rarer and represents the disease with an autosomal recessive pattern of inheritance, caused by calsequestrin (CASQ2) mutations. Some cases of CPVT, even though unusual, have been related to other proteins associated with the calcium homeostasis, which give

origin to the same ventricular arrhythmia pattern. The genes implicated in these recent discoveries are CALM1 (encoding calmodulin) and TRDN (encoding triadin). KCNJ2 and TECRL mutations have been previously described.[10]

The main goal of the therapy is the adrenergic blockade with propranolol or nadolol, which can be reinforced by left cardiac sympathetic denervation in patients who remain symptomatic or with no reduction of PCV and Non-Sustained Ventricular Tachycardia (NSVT) burn during exercise testing. Flecainide, which is not available in Brazil, has been recently shown to have therapeutical benefits by inhibiting ryanodine-mediated calcium release (perhaps propafenone might carry a class effect.[29]

ICD must be indicated mainly in aSCD patients. However, in contrast to other channelopathies, shock may induce release of adrenaline and death by electrical storm and, therefore, pharmacologic optimization is mandatory.[46]

Healthcare in the COVID-19 pandemic

CPVT patients, even if appropriately controlled for symptoms and ventricular arrhythmias, may present with potentially fatal recurrences if β−blockers are withhold or reduced; therefore, it is important to maintain the in- and out-of-hospital medications for these patients, by assessing the hemodynamic status of critically-ill patients.

Medications with α- or β-adrenergic effects, such as vasoactive (epinephrine, noradrenaline) and inotropic (dobutamine, milrinone) drugs, usually employed for hemodynamic support, may increase the risk for ventricular arrhythmias in CPVT patients. Epinephrine is used as a pharmacological test in CPVT due to its potential for unmasking ventricular arrhythmias, and so, if the patient needs hemodynamic support, other vasoactive amines should be preferred to epinephrine.[7,47]

Milrinone, a phosphodiesterase-3 inhibitor, reduces cAMP (cyclic adenosine monophosphate) degradation, thus increasing calcium release by the ryanodine receptor, which is the pathogenesis of CPVT. In some specific situations, and considering the hemodynamic compromise, it may be possible to use a low dose of β−1 receptor blocker (propranolol).[48]

In the course of a severe infection, the patients may not tolerate the chronic use of β−blockers and antiarrhythmics and one must pay attention to hydroelectrolytic disorders during the entire period of greater arrhythmic vulnerability, aiming to avoid them.

Antivirals, such as Ritonavir/Lopinavir, do not show any potential interaction with β−blockers nor a catecholaminergic effect that may increase the arrhythmic risk in CPVT patients; however, they may interact with Flecainide – an adjuvant drug in the treatment of CPVT.[45]

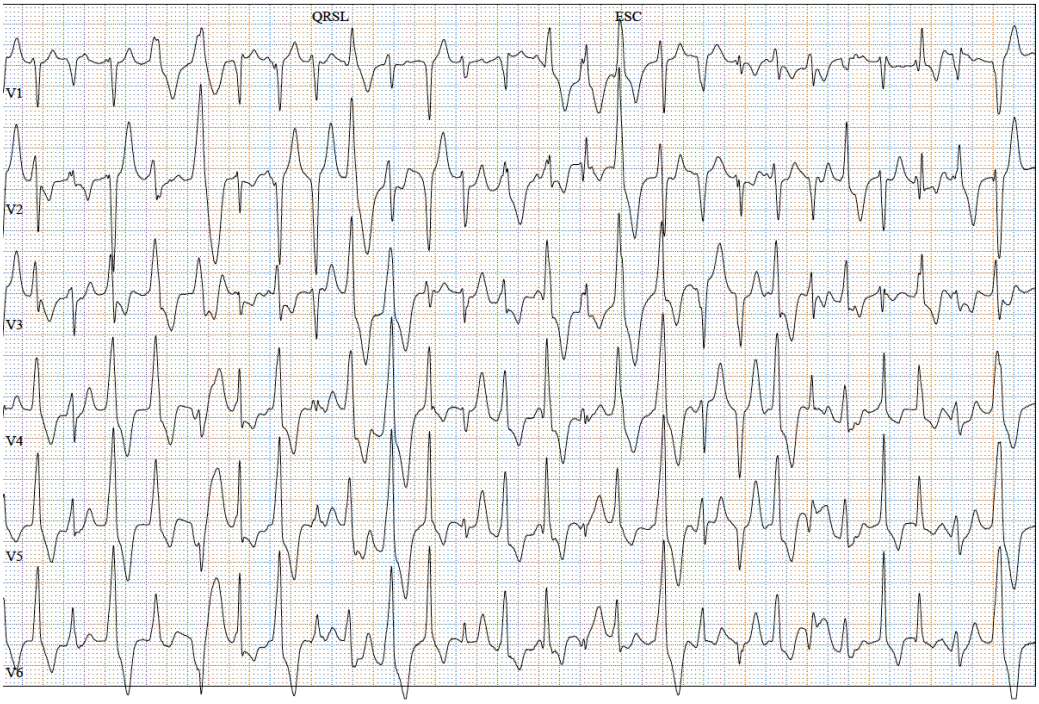


Figure 4 – *Ventricular arrhythmia prototype in patients with Cathecolaminergic Polymorphic Ventricular Tachycardia. A 26-year-old girl with polymorphic premature beats and non-sustained ventricular tachycardia during treadmill test and a family history of sudden cardiac death in the first decade of life. InCor-HCFMUSP collection.*

Hydroxychloroquine apparently does not increase catecholamine levels. However, there is evidence of drug interaction between hydroxychloroquine and propranolol/nadolol. β−blockers are metabolized through cytochrome CYP2D6, and its inhibition by hydroxychloroquine may result in increased concentration of the drug, which demands careful heart rate and blood pressure monitoring.[49] Flecainide and propafenone show a similar interaction, resulting in a serum level increase of the antiarrhythmic drugs and enhancing the arrhythmic risk.[45] In these situations, one must weigh the individual benefit/risk ratio to make a therapeutic decision.

Conclusion

Patients with inherited arrhythmias present with various molecular and structural factors that predispose them to potentially fatal events in the course of a viral infection. The COVID-19 pandemic prompts us to keep these patients away from the risk of infection and to reinforce measures of isolation and hygiene, in addition to orienting healthcare precautions by recalling the peculiarities of carriers of rare diseases. Among the recommendations, we emphasize caution regarding the medications used by the patient, the effective treatment of fever and electrolytic disturbances, and the risk of prescribing medications with proarrhythmic potential.

Author contributions

Conception and design of the research: all authors. Writing of the manuscript: Sacilotto L, Olivetti N. Critical revision of the manuscript for intellectual content: Pisani C, Hachul D, Darrieux F, Scanavacca MI.

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. 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;395(10229):1054-62. doi: 10.1016/S0140-6736(20)30566-3.
2. People with Certain Medical Conditions [Internet]. Washington: Centers for Disease Control and Prevention; 2021 [cited 2021 Jul 12]. Available from: https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html.
3. Wunderink RG, Waterer G. Advances in the Causes and Management of Community Acquired Pneumonia in Adults. BMJ. 2017;358:j2471. doi: 10.1136/bmj.j2471.
4. Corrales-Medina VF, Musher DM, Shachkina S, Chirinos JA. Acute Pneumonia and the Cardiovascular System. Lancet. 2013;381(9865):496-505. doi: 10.1016/S0140-6736(12)61266-5.
5. Marrie TJ, Shariatzadeh MR. Community-Acquired Pneumonia Requiring Admission to an Intensive Care Unit: A Descriptive Study. Medicine. 2007;86(2):103-11. doi: 10.1097/MD.0b013e3180421c16.
6. Carr GE, Yuen TC, McConville JF, Kress JP, VandenHoek TL, Hall JB, et al. Early Cardiac Arrest in Patients Hospitalized With Pneumonia: A Report From the American Heart Association's Get With The Guidelines-Resuscitation Program. Chest. 2012;141(6):1528-36. doi: 10.1378/chest.11-1547.
7. Wu CI, Postema PG, Arbelo E, Behr ER, Bezzina CR, Napolitano C, et al. SARS-CoV-2, COVID-19, and Inherited Arrhythmia Syndromes. Heart Rhythm. 2020;17(9):1456-62. doi: 10.1016/j.hrthm.2020.03.024.
8. Giudicessi JR, Ackerman MJ. Determinants of Incomplete Penetrance and Variable Expressivity in Heritable Cardiac Arrhythmia Syndromes. Transl Res. 2013;161(1):1-14. doi: 10.1016/j.trsl.2012.08.005.
9. Qiu J, Shen B, Zhao M, Wang Z, Xie B, Xu Y. A Nationwide Survey of Psychological Distress Among Chinese People in the COVID-19 Epidemic: Implications and Policy Recommendations. Gen Psychiatr. 2020;33(2):e100213. doi: 10.1136/gpsych-2020-100213.
10. Skinner JR, Winbo A, Abrams D, Vohra J, Wilde AA. Channelopathies That Lead to Sudden Cardiac Death: Clinical and Genetic Aspects. Heart Lung Circ. 2019;28(1):22-30. doi: 10.1016/j.hlc.2018.09.007.
11. 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. doi: 10.1152/physrev.00008.2016.
12. Wu TC, Sacilotto L, Darrieux FCDC, Pisani CF, Melo SL, Hachul DT, et al. QT Interval Control to Prevent Torsades de Pointes during Use of Hydroxychloroquine and/or Azithromycin in Patients with COVID-19. Arq Bras Cardiol. 2020;114(6):1061-6. doi: 10.36660/abc.20200389.
13. Priori SG, Blomström-Lundqvist C, Mazzanti A, Blom N, Borggrefe M, Camm J, et al. 2015 ESC Guidelines for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: The Task Force for the Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death of the European Society of Cardiology (ESC). Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC). Eur Heart J. 2015;36(41):2793-867. doi: 10.1093/eurheartj/ehv316.
14. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS Guideline for Management of Patients with Ventricular Arrhythmias and the Prevention of Sudden Cardiac Death: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm. 2018;15(10):190-252. doi: 10.1016/j.hrthm.2017.10.035.
15. Amin AS, Herfst LJ, Delisle BP, Klemens CA, Rook MB, Bezzina CR, et al. Fever-Induced QTc Prolongation and Ventricular Arrhythmias in Individuals with type 2 Congenital Long QT Syndrome. J Clin Invest. 2008;118(7):2552-61. doi: 10.1172/JCI35337.
16. Salinas P, Lopez-de-Sa E, Pena-Conde L, Viana-Tejedor A, Rey-Blas JR, Armada E, et al. Electrocardiographic Changes During Induced Therapeutic Hypothermia in Comatose Survivors After Cardiac Arrest. World J Cardiol. 2015;7(7):423-30. doi: 10.4330/wjc.v7.i7.423.

17. El-Sherif N, Turitto G, Boutjdir M. Acquired Long QT Syndrome and Torsade de Pointes. Pacing Clin Electrophysiol. 2018;41(4):414-21. doi: 10.1111/pace.13296.

18. Lazzerini PE, Capecchi PL, Laghi-Pasini F, Boutjdir M. Autoimmune Channelopathies as a Novel Mechanism in Cardiac Arrhythmias. Nat Rev Cardiol. 2017;14(9):521-35. doi: 10.1038/nrcardio.2017.61.

19. Giudicessi JR, Ackerman MJ, Camilleri M. Cardiovascular Safety of Prokinetic Agents: A Focus on Drug-Induced Arrhythmias. Neurogastroenterol Motil. 2018;30(6):e13302. doi: 10.1111/nmo.13302.

20. O'Hare M, Maldonado Y, Munro J, Ackerman MJ, Ramakrishna H, Sorajja D. Perioperative Management of Patients with Congenital or Acquired Disorders of the QT Interval. Br J Anaesth. 2018;120(4):629-44. doi: 10.1016/j.bja.2017.12.040.

21. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Clin Infect Dis. 2020;71(15):732-9. doi: 10.1093/cid/ciaa237.

22. Mazzanti A, Briani M, Kukavica D, Bulian F, Marelli S, Trancuccio A, et al. Association of Hydroxychloroquine With QTc Interval in Patients with COVID-19. Circulation. 2020;142(5):513-5. doi: 10.1161/CIRCULATIONAHA.120.048476.

23. Teixeira RA, Borba EF, Pedrosa A, Nishioka S, Viana VS, Ramires JA, et al. Evidence for Cardiac Safety and Antiarrhythmic Potential of Chloroquine in Systemic Lupus Erythematosus. Europace. 2014;16(6):887-92. doi: 10.1093/europace/eut290.

24. Viskin S. Long QT Syndromes and Torsade de Pointes. Lancet. 1999;354(9190):1625-33. doi: 10.1016/S0140-6736(99)02107-8.

25. Morrison LJ, Deakin CD, Morley PT, Callaway CW, Kerber RE, Kronick SL, et al. Part 8: Advanced Life Support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. Circulation. 2010;122(16 Suppl 2):345-421. doi: 10.1161/CIRCULATIONAHA.110.971051.

26. Kawada S, Morita H, Antzelevitch C, Morimoto Y, Nakagawa K, Watanabe A, et al. Shanghai Score System for Diagnosis of Brugada Syndrome: Validation of the Score System and System and Reclassification of the Patients. JACC Clin Electrophysiol. 2018;4(6):724-30. doi: 10.1016/j.jacep.2018.02.009.

27. Oliveira Neto NR, Oliveira WS, Mastrocola F, Sacilotto L. Brugada Phenocopy: Mechanisms, Diagnosis, and Implications. J Electrocardiol. 2019;55:45-50. doi: 10.1016/j.jelectrocard.2019.04.017.

28. Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present Status of Brugada Syndrome: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018;72(9):1046-59. doi: 10.1016/j.jacc.2018.06.037.

29. Al-Khatib SM, Stevenson WG, Ackerman MJ, Bryant WJ, Callans DJ, Curtis AB, et al. 2017 AHA/ACC/HRS guideline for management of patients with ventricular arrhythmias and the prevention of sudden cardiac death: Executive summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. Heart Rhythm. 2018;15(10):e190-e252. doi: 10.1016/j.hrthm.2017.10.035.

30. Michowitz Y, Milman A, Sarquella-Brugada G, Andorin A, Champagne J, Postema PG, et al. Fever-Related Arrhythmic Events in the Multicenter Survey on Arrhythmic Events in Brugada Syndrome. Heart Rhythm. 2018;15(9):1394-401. doi: 10.1016/j.hrthm.2018.04.007.

31. Chang D, Saleh M, Garcia-Bengo Y, Choi E, Epstein L, Willner J. COVID-19 Infection Unmasking Brugada Syndrome. HeartRhythm Case Rep. 2020;6(5):237-40. doi: 10.1016/j.hrcr.2020.03.012.

32. White NJ. Cardiotoxicity of Antimalarial Drugs. Lancet Infect Dis. 2007;7(8):549-58. doi: 10.1016/S1473-3099(07)70187-1.

33. Szél T, Koncz I, Antzelevitch C. Cellular Mechanisms Underlying the Effects of Milrinone and Cilostazol to Suppress Arrhythmogenesis Associated with Brugada syndrome. Heart Rhythm. 2013;10(11):1720-7. doi: 10.1016/j.hrthm.2013.07.047.

34. Peters S, Trümmel M, Meyners W. Prevalence of Right Ventricular Dysplasia-Cardiomyopathy in a Non-Referral Hospital. Int J Cardiol. 2004;97(3):499-501. doi: 10.1016/j.ijcard.2003.10.037.

35. Towbin JA, McKenna WJ, Abrams DJ, Ackerman MJ, Calkins H, Darrieux FCC, et al. 2019 HRS Expert Consensus Statement on Evaluation, Risk Stratification, and Management of Arrhythmogenic Cardiomyopathy: Executive Summary. Heart Rhythm. 2019;16(11):373-407. doi: 10.1016/j.hrthm.2019.09.019.

36. McKoy G, Protonotarios N, Crosby A, Tsatsopoulou A, Anastasakis A, Coonar A, et al. Identification of a Deletion in Plakoglobin in Arrhythmogenic Right Ventricular Cardiomyopathy with Palmoplantar Keratoderma and Woolly Hair (Naxos disease). Lancet. 2000;355(9221):2119-24. doi: 10.1016/S0140-6736(00)02379-5.

37. Norgett EE, Hatsell SJ, Carvajal-Huerta L, Cabezas JC, Common J, Purkis PE, et al. Recessive Mutation in Desmoplakin Disrupts Desmoplakin-Intermediate Filament Interactions and Causes Dilated Cardiomyopathy, Woolly Hair and Keratoderma. Hum Mol Genet. 2000;9(18):2761-6. doi: 10.1093/hmg/9.18.2761.

38. Bhonsale A, Groeneweg JA, James CA, Dooijes D, Tichnell C, Jongbloed JD, et al. Impact of Genotype on Clinical Course in Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy-Associated Mutation Carriers. Eur Heart J. 2015;36(14):847-55. doi: 10.1093/eurheartj/ehu509.

39. Groeneweg JA, Bhonsale A, James CA, Riele AS, Dooijes D, Tichnell C, et al. Clinical Presentation, Long-Term Follow-Up, and Outcomes of 1001 Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy Patients and Family Members. Circ Cardiovasc Genet. 2015;8(3):437-46. doi: 10.1161/CIRCGENETICS.114.001003.

40. Basso C, Czarnowska E, Barbera MD, Bauce B, Beffagna G, Wlodarska EK, et al. Ultrastructural Evidence of Intercalated Disc Remodelling in Arrhythmogenic Right Ventricular Cardiomyopathy: An Electron Microscopy Investigation on Endomyocardial Biopsies. Eur Heart J. 2006;27(15):1847-54. doi: 10.1093/eurheartj/ehl095.

41. Fontaine G, Frank R, Tonet JL, Guiraudon G, Cabrol C, Chomette G, et al. Arrhythmogenic Right Ventricular Dysplasia: A Clinical Model for the Study of Chronic Ventricular Tachycardia. Jpn Circ J. 1984;48(6):515-38. doi: 10.1253/jcj.48.515.

42. Corrado D, Wichter T, Link MS, Hauer R, Marchlinski F, Anastasakis A, et al. Treatment of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia: An International Task Force Consensus Statement. Eur Heart J. 2015;36(46):3227-37. doi: 10.1093/eurheartj/ehv162.

43. Wang XT, Liu DW, Zhang HM, Long Y, Guan XD, Qiu HB, et al. Experts consensus on the management of the right heart function in critically ill patients. Zhonghua Nei Ke Za Zhi. 2017;56(12):962-73. doi: 10.3760/cma.j.issn.0578-1426.2017.12.017.

44. Aimo A, Baritussio A, Emdin M, Tascini C. Amiodarone as a Possible Therapy for Coronavirus Infection. Eur J Prev Cardiol. 2020:2047487320919233. doi: 10.1177/2047487320919233.

45. Giudicessi JR, Noseworthy PA, Friedman PA, Ackerman MJ. Urgent Guidance for Navigating and Circumventing the QTc-Prolonging and Torsadogenic Potential of Possible Pharmacotherapies for Coronavirus Disease 19 (COVID-19). Mayo Clin Proc. 2020;95(6):1213-21. doi: 10.1016/j.mayocp.2020.03.024.

46. Marai I, Khoury A, Suleiman M, Gepstein L, Blich M, Lorber A, et al. Importance of Ventricular Tachycardia Storms Not Terminated by Implantable Cardioverter Defibrillators Shocks in Patients with CASQ2 Associated Catecholaminergic Polymorphic Ventricular Tachycardia. Am J Cardiol. 2012;110(1):72-6. doi: 10.1016/j.amjcard.2012.02.049.

47. Marjamaa A, Hiippala A, Arrhenius B, Lahtinen AM, Kontula K, Toivonen L, et al. Intravenous Epinephrine Infusion Test in Diagnosis of Catecholaminergic Polymorphic Ventricular Tachycardia. J Cardiovasc Electrophysiol. 2012;23(2):194-9. doi: 10.1111/j.1540-8167.2011.02188.x.

48. Kobayashi S, Susa T, Ishiguchi H, Myoren T, Murakami W, Kato T, et al. A Low-Dose β1-Blocker in Combination with Milrinone Improves Intracellular Ca2+ Handling in Failing Cardiomyocytes by Inhibition of Milrinone-Induced Diastolic Ca2+ Leakage from the Sarcoplasmic Reticulum. PLoS One. 2015;10(1):e0114314. doi: 10.1371/journal.pone.0114314.

49. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Biondi-Zoccai G, et al. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the COVID-19 Pandemic. J Am Coll Cardiol. 2020;75(18):2352-71. doi: 10.1016/j.jacc.2020.03.031.

50. brugadadrugs.org [Internet]. Amsterdã: Amsterdam University Medical Centers; 2021 [cited 2021 Jul 12]. Available from: https://www.brugadadrugs.org/

Patient in Cardiorespiratory Arrest - Is it Possible to Perform Transcatheter Aortic Valve Implantation (TAVI) in this Scenario?

Alexandre de Matos Soeiro,[1] Francisco Akira Cardozo,[1] Patrícia Oliveira Guimarães,[1] Marcel Paula Pereira,[1] Paulo Vinícius Ramos Souza,[1] Gustavo A. B. Boros,[1] Viviane Cordeiro Veiga,[1] Samolon Soriano Ordinola Rojas,[1] Fernanda Marinho Mangione,[1] Salvador André Bavaresco Cristóvão,[1] Gustavo Alexandre Dutra,[1] Adnan Ali Salman,[1] Luiz Eduardo Loureiro Bettarello,[1] José Armando Mangione[1]

Hospital Beneficência Portuguesa de São Paulo - Unidade Cardiológica Intensiva,[1] São Paulo, SP – Brazil

Introduction

Transcatheter aortic valve implantation (TAVI) is a well-established procedure in reference centers worldwide and is currently accepted as the method of choice in high- and intermediate-risk patients. Although unusual, catastrophic complications can occur before or after its implantation, such as coronary obstruction, rupture of the aortic valve annulus, cardiac tamponade, significant perivalvular insufficiency and prosthesis embolization/displacement.

Data from a recently published North American registry showed that 1,695 patients (2.8%) undergoing TAVI required some type of mechanical circulatory support during hospitalization. It was observed that heart failure, transapical access, respiratory diseases, acute myocardial infarction, cardiorespiratory arrest (CRA) and cardiogenic shock were the factors most frequently associated with the need for mechanical circulatory support.[1]

Although its use is widespread, mainly in high-risk patients, and the main complications of the method and the underlying disease are already known, its use in CRA is not yet indicated and to date, rarely described in the literature.[1] Implantation during CRA makes the technique difficult due to chest compressions, impossibility of assessing the immediate result and limited time for effective expansion of the prosthesis.

In 2013, the use of mechanical compression (AutoPulse) was described for the first time during the occurrence of CRA after the start of TAVI as a safe and effective alternative, allowing the procedure to be carried out until its completion.[2] In 2014, another case report showed the possibility of deformation of the prosthesis after manual CPR, which progressed with significant paravalvular leak and subsequent death.[3]

Based on these possibilities of complications, there are protocols for indicating extracorporeal membrane oxygenation (ECMO) in patients undergoing TAVI who progress to cardiogenic shock or even CRA. In high-risk cases, some services have organized and managed to place patients who progress to CRA during TAVI on ECMO in up to 5 minutes. This allows the rapid stabilization of the patient before the occurrence of multiple-organ dysfunction and even carrying out the procedure to the end.[4]

Thus, reports of complications and CRA associated with TAVI have only been described during or after the endoprosthesis expansion procedure. The aim of the present case is to share the success and pioneering spirit of a Brazilian reference center in TAVI performance in a patient with pre-procedural CRA as a rescue measure.

Description

An 84-year-old female patient had started having dyspnea at rest 6 days before. She reported a personal history of systemic arterial hypertension, dyslipidemia and acute myocardial infarction, at which point a percutaneous coronary intervention was performed with drug-eluting stent in the left main coronary artery and circumflex artery two months before. She was initially admitted via the emergency department of a secondary hospital. At admission, she was in poor overall health status, with tachycardia (heart rate = 120 bpm), tachypnea (respiratory rate = 28 bpm), blood pressure of 76x40 mmHg, and increased capillary refill time (6 seconds). Cardiac auscultation showed rhythmic heart sounds with systolic ejection heart murmur in aortic focus, +3/+6, and vesicular murmurs present with rales up to the middle third bilaterally on pulmonary auscultation. Initially, intravenous furosemide, norepinephrine and dobutamine were started in continuous infusion, in addition to the use of non-invasive ventilation.

The electrocardiogram did not show acute ischemic alterations and myocardial necrosis markers were negative. Additionally, an initial screening did not show any changes suggestive of an infectious condition. At that time, a transthoracic echocardiogram was requested, which showed a left ventricular ejection fraction of 28% with diffuse hypokinesia, calcified aortic valve, with a valve area of 0.6 cm^2 and a maximum left ventricle-aorta gradient of 66 mmHg and a mean of 35 mmHg, in addition to moderate mitral regurgitation (Figure 1).

After two failed attempts at weaning the patient from vasoactive drugs, it was decided to transfer the patient to a tertiary center using intensive care air transport. After the initial assessment and based on the risk associated with the patient, transfemoral TAVI was indicated. After 72 hours in the high-complexity hospital, the patient showed worsening of cardiogenic shock and the need for a progressive increase in vasoactive drugs (dobutamine 20 μg/kg/min and norepinephrine 0.3 μg/kg/min). Therefore, the patient

Keywords

Aortic Valve; Heart Arrest; Emergencies; Cardiogenic Shock

Mailing Address: Alexandre de Matos Soeiro •
Av. Dr. Enéas de Carvalho Aguiar, 44. Postal Code 09541001, São Paulo, SP – Brazil
E-mail: alexandre.soeiro@bol.com.br
Manuscript received October 12, 2020, revised manuscript December 02, 2020, accepted December 02, 2020

DOI: https://doi.org/10.36660/abc.20201097

Research Letter

was urgently transferred to the hemodynamics laboratory to undergo the percutaneous procedure. The patient was placed in the horizontal decubitus position, and the orotracheal intubation, asepsis procedure and femoral access were performed. At the start of the transvenous pacemaker lead introduction, the patient showed CRA with ventricular fibrillation rhythm with rapid degeneration to asystole. Cardiopulmonary resuscitation (CPR) measures were initiated in accordance with advanced cardiology life support (ACLS) guidelines. At that moment, as a rescue measure, during CPR and without the aid of the echocardiogram, TAVI was performed with the Edwards SAPIEN 3 prosthesis N. 26 only with scope visualization in the room, with a total procedure time of 4 minutes (Figure 2). Immediately after that, the patient returned to spontaneous circulation rhythm. During the early post-procedure period, the patient progressed with worsening of cardiogenic shock, requiring increased doses of norepinephrine, use of vasopressin and intra-aortic balloon pump. A new transthoracic echocardiogram showed a left ventricular ejection fraction of 33% with diffuse hypokinesia, prosthesis in the aortic position, with a maximum left ventricle-aorta gradient of 35 mmHg and a mean gradient of 17 mmHg, with mild to moderate peri-prosthesis aortic insufficiency (Figure 3).

After 48 hours, the patient showed improvement in hemodynamic parameters, and was progressively weaned from mechanical support and vasoactive drugs and submitted to extubation on the seventh day after TAVI, remaining without neurological deficits. She was discharged from the hospital after 28 days of an asymptomatic hospitalization from a cardiovascular viewpoint.

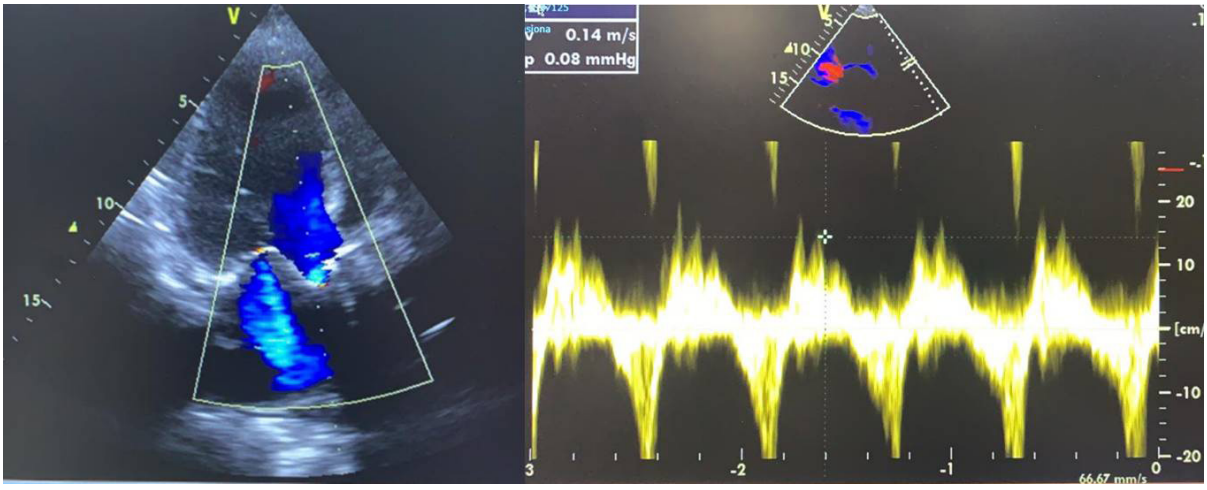


Figure 1 – *Transthoracic echocardiogram in pre-TAVI apical window showing a calcified aortic valve, with valvular area of 0.6 cm² and maximum left ventricle-aorta gradient of 66 mmHg and mean gradient of 35 mmHg.*

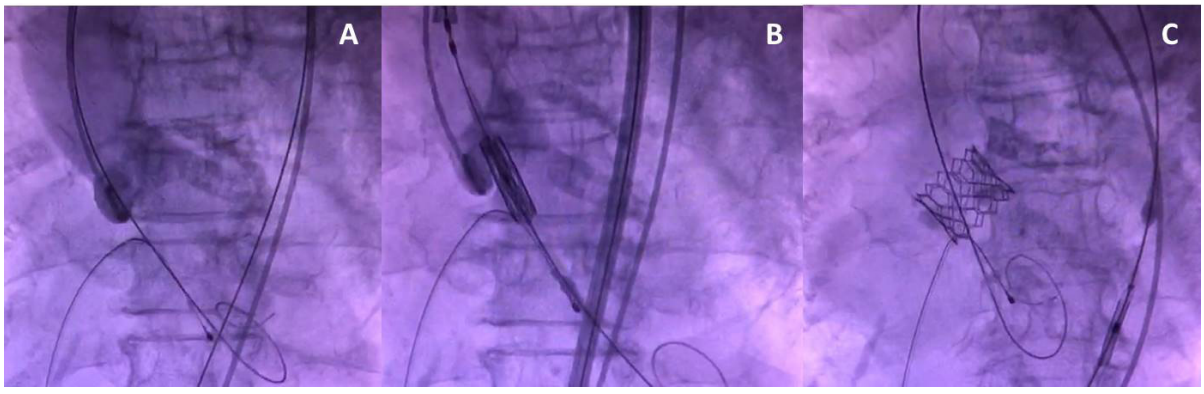


Figure 2 – *TAVI was performed with an Edwards SAPIEN 3 prosthesis n. 26, with scope visualization only, during CPR maneuvers. A) Positioning of catheters; B) Alignment of the prosthesis in the aortic valve annulus; C) Prosthesis shown in the aortic position.*

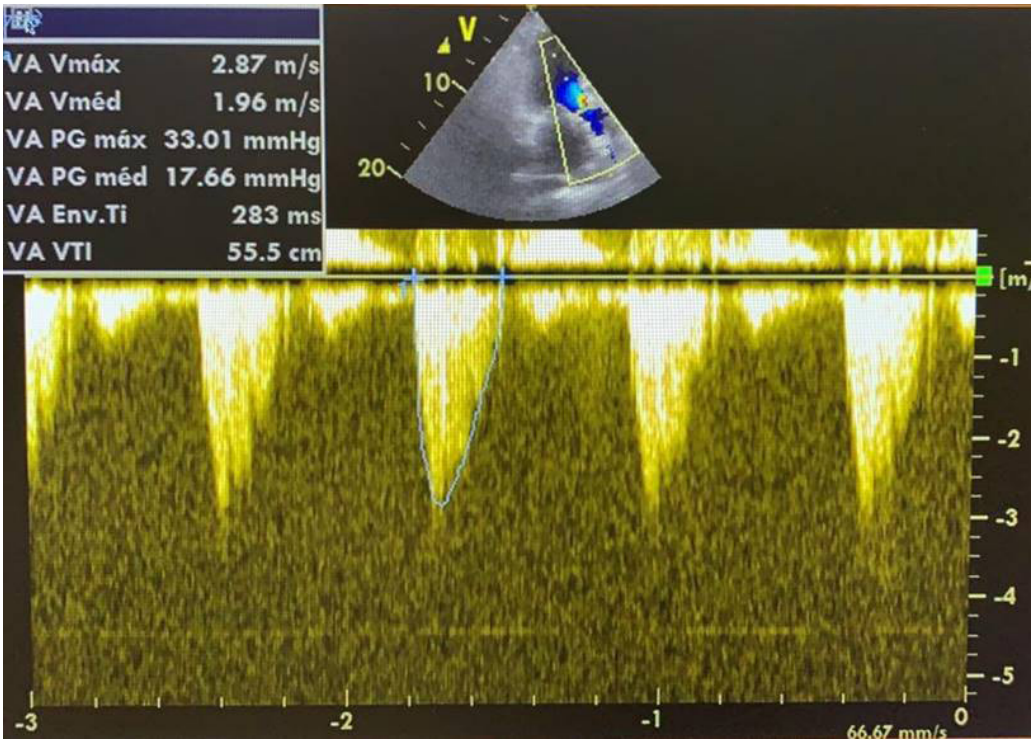


Figure 3 – *Transthoracic echocardiogram after TAVI, showing a left ventricular ejection fraction of 33%, prosthesis in the aortic position with a maximum left ventricle-aortic gradient of 35 mmHg and a mean gradient of 17 mmHg, with mild to moderate peri-prosthesis aortic insufficiency.*

Author Contributions

Conception and design of the research: Soeiro AM, Guimarães PO, Pereira MP, Veiga VC, Mangione FM, Dutra GA, Salman AA; Boros GAB; Acquisition of data: Soeiro AM, Cardozo FA, Guimarães PO, Pereira MP, Veiga VC; Analysis and interpretation of the data: Soeiro AM, Pereira MP; Writing of the manuscript: Soeiro AM, Cardozo FA, Guimarães PO, Souza PVR, Mangione FM; Critical revision of the manuscript for intellectual content: Veiga VC, Rojas SSO, Cristóvão SAB, Dutra GA, Salman AA, Bettarello LEL, Mangione JA. Supervision: Gustavo A. B. Boros.

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. Alkhalil A, Hajjar R, Ibrahim H, Ruiz CE. Mechanical circulatory support in transcatheter aortic valve implantation in the United States (from the National Inpatient Sample). Am J Cardiol. 2019;124(10):1615-20. doi: 10.1016/j.amjcard.2019.08.013.
2. Satler LF, Pichard AD. The use of automated chest compression for arrest during TAVI. Catheter Cardiovasc Interv. 2013;82(5):849-50. doi: 10.1002/ccd.24968.
3. Kim EK, Choi SH, Song PS, Park SJ. Valve prosthesis distortion after cardiac compression in a patient who underwent transcatheter aortic valve implantation (TAVI). Catheter Cardiovasc Interv. 2014;83(3):165-7. doi: 10.1002/ccd.24412.
4. Fernandes P, Cleland A, Bainbridge D, Jones PM, Chu MW, Kiaii B. Development of our TAVI protocol for emergency initiation of cardiopulmonary bypass. Perfusion. 2015;30(1):34-9. doi: 10.1177/0267659114547754.

Unusual Finding of Rare Exuberant Xanthomatosis in Hyperlipidemia

Enrico Manfredini[1] *and Renato Jorge Alves*[1,2]

Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSCSP),[1] *São Paulo, SP - Brazil*

Irmandade da Santa Casa de Misericórdia de São Paulo - Departamento de Medicina,[2] *São Paulo, SP – Brazil*

Introduction

Hyperlipidemia can increase morbidity and mortality. This condition has been classified by Fredrickson into the following phenotypes: I, IIa, IIb, III, IV and V.[1-5] In the mixed ones, the following conditions are present: hypercholesterolemia and hypertriglyceridemia, phenotypes IIb and III, with cholesterolemia and triglyceridemia of 250 to 300 mg/dL in phenotype IIb, and 500 to 600 mg/dL or more, in III, respectively. Pancreatitis is uncommon in both, as well as xanthomatosis in IIb. Xanthomas and cardiovascular complications are more frequent in phenotype III.[2,6]

We present a case of hyperlipidemia with relevant lipid abnormalities, pancreatitis and exuberant xanthomatosis.

Case Report

Male, 48 years old, born in Manaus, retailer, with a history of hemorrhagic pancreatitis (2004), arterial hypertension and type 2 diabetes since 2006, grade 3 hypertensive retinopathy and severe proliferative diabetic retinopathy. Denied family history of cardiovascular disease or dyslipidemia and denied consanguinity in the family. Used enalapril 10 mg/day, dapagliflozin 5 mg/day, metformin 1000 mg/day, gliclazide 120 mg/day and NPH insulin 16 UI/day. Denied previous use of statin, only fibrate irregularly.

Asymptomatic and anicteric. Weight: 89 Kg, height: 172 cm, BMI: 30.1 kg/m^2, blood pressure: 120/90 mmHg, heart rate: 80 bpm. Clean lungs, normophonetic rhythmic heart sounds, protosystolic murmur in aortic area 2/6+, no carotid murmurs. Regular and unaltered distal pulses. Distended abdomen with umbilical scar. Lower limbs with no edema.

Presence of multiple extensive painless nodular lesions in the elbows, bilateral metacarpophalangeal and interphalangeal joints, knees and ankles, compatible with tuberous and tendinous xanthomas (Figure 1). No striated palmar xanthoma.

Lipoprotein electrophoresis was performed: alpha fraction 6.2%, beta and pre-beta 93.8%, compatible with phenotype IIb.

Keywords

Hyperlipidemias; Dyslipidemias; Xanthomatosis; Hypolipidemic Agents.

Mailing Address: Renato Jorge Alves •
Faculdade de Ciências Médicas da Santa Casa de São Paulo (FCMSCSP) - Rua Dr. Cesário Mota Júnior, 112. Postal Code 01221-020, Santa Cecilia, São Paulo, SP – Brazil
E-mail: renatoalves178@gmail.com
Manuscript received September 17, 2020, revised manuscript February 04, 2021, accepted February 24, 2021

DOI: https://doi.org/10.36660/abc.20200999

Due to hyperlipidemia, it was decided to introduce atorvastatin 40, after 6 months, 80 mg/day, and ciprofibrate 100 mg/day, associated with lifestyle modifications and diet therapy. After this therapy, there was a significant regression of xanthomatous lesions (Figure 2) and hyperlipidemia (Table 1).

Discussion

This is an uncommon finding of diffuse xanthomatosis in a patient with the IIb phenotype, which usually migrates to IIa and IV in clinical practice.

This xanthomatosis is rarely seen in the IIb phenotype, especially the tuberous form in the Achilles tendon, more commonly found in familial hypercholesterolemia (FH).[7] Echocardiogram showed calcification of the aortic valve, also found in severe cases of FH or lipoprotein plasma elevation(a) – Lp(a).[8,9] However, a very satisfactory response to statin therapy, as occurred in this case, would not be common in FH, especially in the homozygous form.[1,3]

Marked hypertriglyceridemia would indicate phenotype IV or V; however, lipoprotein electrophoresis showed elevations in beta and pre-beta fractions.[6] However, hypertriglyceridemia >1500 mg/dL with tuberous and tendinous xanthomas would be compatible with mixed dyslipidemia.[2,6]

In phenotype III, in addition to tuberous and eruptive xanthomatosis, there would be palmar xanthomatosis and early atherosclerotic disease.[9] Furthermore, plasma concentrations of cholesterol and triglycerides would be very high, but almost similar. However, because the metabolic disorders have contributed to worsening of the condition and the xanthomas resemble tuberoeruptive xanthomatosis, dysbetalipoproteinemia (type III) associated with genetic defects such as FH or Lp(a) elevation, it would be the appropriate hypothesis to be considered.

Other ruled out hypotheses would be: cerebrotendinous xanthomatosis, no neurological alterations,[10,11] and sitosterolemia, due to a satisfactory response with statin,[12,13] although it could be ruled out by genotyping.

It is relevant to report the occurrence of acute pancreatitis in 2004, with consequent diabetes, more frequent in phenotype I than in V.[2,6,14] In this case, diagnosis of diabetes occurred after report of pancreatitis, suggesting relevant hypertriglyceridemia, due to genetic or environmental causes, as the patient was not fully following the fibrate therapy.

The dyslipidemia phenotype is not always clear, even with complementary tests, making difficult to deliver early diagnosis and conduct appropriate management.[15]

Association of statin (high potency) and ciprofibrate achieved the expected objective, as seen in the laboratory results and the healing of xanthomas. If low-density lipoprotein (LDL-c) targets were not met, the association of statin

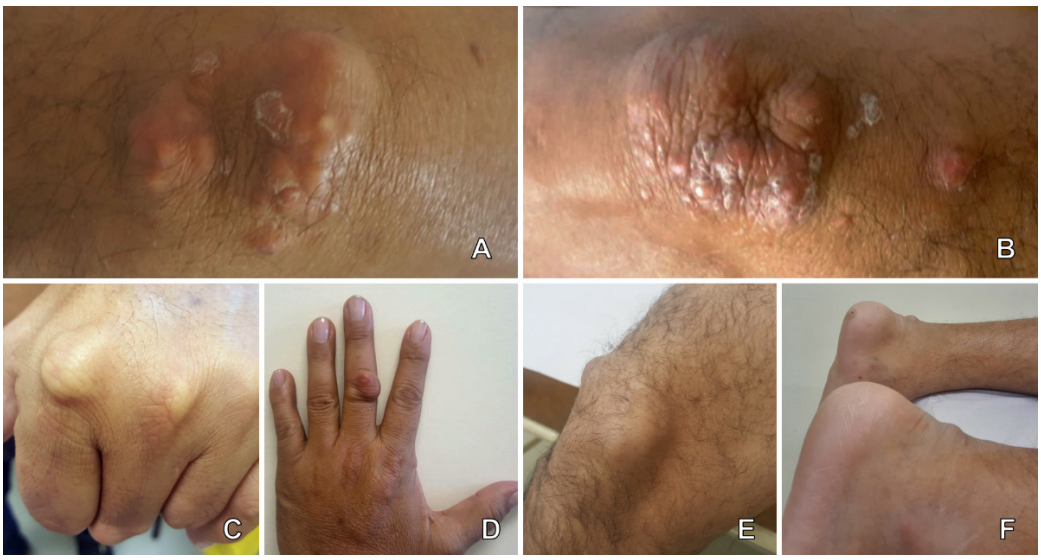


Figure 1 – *Previous xanthomatosis: A) Right elbow; B) Left elbow; C) Second joint left metacarpophalangeal; D) Third right proximal interphalangeal joint; E) Right knee; F) Both Achilles tendons. Source: images taken by the authors at a routine appointment.*

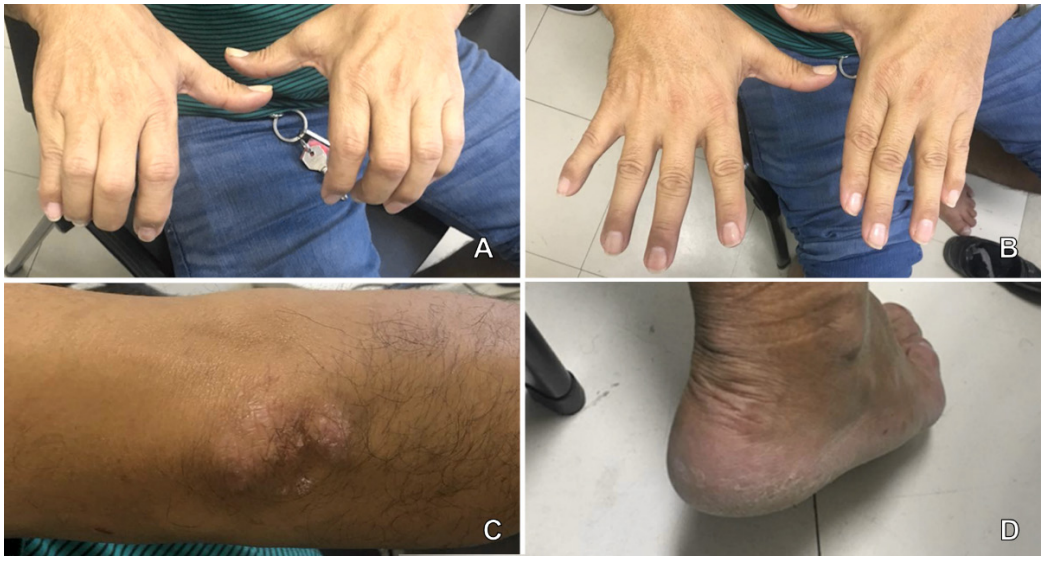


Figure 2 – *Regression of xanthomas: A and B) Interphalangeal and metacarpophalangeal joints; C) Right elbow; D) Right Achilles tendon region. Source: images taken by the authors at a routine appointment.*

with proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors or ezetimibe would be an option, as would omega-3 with fibrate to reduce hypertriglyceridemia.[2]

As limitations, due to unavailability in the institution, we did not perform: coronary angiotomography to better stratify cardiovascular risk,[2,16] although the patient is at high risk,[9] and genetic tests to assess possible mutations in lipoprotein lipase and apolipoprotein E. Despite this, clinical and laboratory evaluation combined with the experience of the service were essential for a satisfactory result, avoiding an atherosclerotic outcome or a new pancreatitis. Although increasingly present, genotyping is not widely available in many countries and services.[17,18]

Table 1 – Laboratory tests

Laboratory tests	Before treatment	After treatment
Triglycerides	2407 mg/dL	291 mg/dL
Total cholesterol	513 mg/dL	144 mg/dL
HDL-c	40 mg/dL	36 mg/dL
LDL-c	NC	50 mg/dL
Glucose	234 mg/dL	137 mg/dL
Glycated hemoglobin	10%	7,1%
GOT	12 U/L	13 U/L
ALT	21 U/L	7 U/L
TSH	4.27 mU/L	3.62 mU/L
CPK	VI	74 U/L
Creatinine	0.7 mg/dL	VI
Uric acid	VI	6.4 mg/dL

HDL: High-density lipoprotein; LDL: low-density lipoprotein; NC: not calculated by Friedewald's Formula; VI: unavailable; GOT: glutamic oxaloacetic transaminase; ALT: alanine transaminase; TSH: thyroid stimulating hormone; CPK: creatine phosphokinase. Source: review of medical records by the authors.

Conclusion

Despite the difficulties found in laboratory investigation, expertise in detecting and adequately treating a rare and severe case of dyslipidemia was essential for laboratory improvement and to prevent potentially fatal clinical outcomes.

Author Contributions

Conception and design of the research, Acquisition of data, Analysis and interpretation of the data, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Manfredini E, Alves RJ.

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 Santa Casa de Misericórdia de São Paulo under the protocol number CAAE: 23019019.3.0000.5479. 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. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;139(25):1082-143. doi: 10.1161/CIR.0000000000000625.
2. Faludi AA, Izar MCO, Saraiva JFK, Chacra APM, Bianco HT, Afiune A Neto, et al. Atualização da Diretriz Brasileira de Dislipidemias e Prevenção da Aterosclerose – 2017. Arq Bras Cardiol. 2017;109(2 Supl 1):1-76. doi: 10.5935/abc.20170121.
3. Santos RD, Gagliardi AC, Xavier HT, Casella A Filho, Araújo DB, Cesena FY, et al. First Brazilian Guidelines for Familial Hypercholesterolemia. Arq Bras Cardiol. 2012;99(2 Suppl 2):1-28. doi: 10.5935/abc.20120202.
4. Fredrickson DS, Levy RI, Lees RS. Fat Transport in Lipoproteins — An Integrated Approach to Mechanisms and Disorders. N Engl J Med. 1967;276(1):34-42. doi: 10.1056/NEJM196701052760107.
5. Fredrickson DS, Lees RS. A System for Phenotyping Hyperlipoproteinemia. Circulation. 1965;31:321-7. doi: 10.1161/01.cir.31.3.321.
6. Hegele RA, Ginsberg HN, Chapman MJ, Nordestgaard BG, Kuivenhoven JA, Averna M, et al. The Polygenic Nature of Hypertriglyceridaemia: Implications for Definition, Diagnosis, and Management. Lancet Diabetes Endocrinol. 2014;2(8):655-66. doi: 10.1016/S2213-8587(13)70191-8.
7. Hopkins PN, Toth PP, Ballantyne CM, Rader DJ. Familial Hypercholesterolemias: Prevalence, Genetics, Diagnosis and Screening Recommendations from the National Lipid Association Expert Panel on

Familial Hypercholesterolemia. J Clin Lipidol. 2011;5(3 Suppl):9-17. doi: 10.1016/j.jacl.2011.03.452.

8. Kate GJRT, Bos S, Dedic A, Neefjes LA, Kurata A, Langendonk JG, et al. Increased Aortic Valve Calcification in Familial Hypercholesterolemia: Prevalence, Extent, and Associated Risk Factors. J Am Coll Cardiol. 2015;66(24):2687-95. doi: 10.1016/j.jacc.2015.09.087.

9. Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias: Lipid Modification to Reduce Cardiovascular Risk. Eur Heart J. 2020;41(1):111-88. doi: 10.1093/eurheartj/ehz455.

10. Keren Z, Falik-Zaccai TC. Cerebrotendinous Xanthomatosis (CTX): A Treatable Lipid Storage Disease. Pediatr Endocrinol Rev. 2009;7(1):6-11.

11. Nie S, Chen G, Cao X, Zhang Y. Cerebrotendinous Xanthomatosis: A Comprehensive Review of Pathogenesis, Clinical Manifestations, Diagnosis, and Management. Orphanet J Rare Dis. 2014;9:179. doi: 10.1186/s13023-014-0179-4.

12. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents; National Heart, Lung, and Blood Institute. Expert Panel on Integrated Guidelines for Cardiovascular Health and Risk Reduction in Children and Adolescents: Summary Report. Pediatrics. 2011;128 (Suppl 5):213-56. doi: 10.1542/peds.2009-2107C.

13. Yoo EG. Sitosterolemia: A Review and Update of Pathophysiology, Clinical Spectrum, Diagnosis, and Management. Ann Pediatr Endocrinol Metab. 2016;21(1):7-14. doi: 10.6065/apem.2016.21.1.7.

14. Scherer J, Singh VP, Pitchumoni CS, Yadav D. Issues in Hypertriglyceridemic Pancreatitis: An Update. J Clin Gastroenterol. 2014;48(3):195-203. doi: 10.1097/01.mcg.0000436438.60145.5a.

15. García-Giustiniani D, Stein R. Genetics of Dyslipidemia. Arq Bras Cardiol. 2016;106(5):434-8. doi: 10.5935/abc.20160074.

16. Pearson TA, Mensah GA, Alexander RW, Anderson JL, Cannon RO 3rd, Criqui M, et al. Markers of Inflammation and Cardiovascular Disease: Application to Clinical and Public Health Practice: A Statement for Healthcare Professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation. 2003;107(3):499-511. doi: 10.1161/01.cir.0000052939.59093.45.

17. Stein R, Ferrari F, Scolari F. Genetics, Dyslipidemia, and Cardiovascular Disease: New Insights. Curr Cardiol Rep. 2019;21(8):68. doi: 10.1007/s11886-019-1161-5.

18. Berberich AJ, Hegele RA. The Role of Genetic Testing in Dyslipidaemia. Pathology. 2019;51(2):184-92. doi: 10.1016/j.pathol.2018.10.014.

SARS-CoV-2 and Myocardical Injury with ST-Elevation without Coronary Disease

Carolina Ragonetti,[1] Enzo Oku Martinazzo,[1] Felipe Montesano Fazionato,[1] Guilherme Osório Guimarães Ferreira,[1] Milena Piccolo Santana,[1] Camila Hartmann[1,2]

Pontifícia Universidade Católica do Paraná,[1] Curitiba, PR - Brazil
Hospital Marcelino Champagnat,[2] Curitiba, PR - Brazil

Introduction

Throughout the SARS-CoV-2 pandemic, there have been reports of infection leading to acute myocardial injury, causing worse clinical outcomes. The manifestations can include troponin elevation, imaging exam abnormalities and electrocardiographic changes.[1] Accordingly, ST-segment elevation (STE) acute myocardial injury has been observed in some patients. However, despite the electrocardiogram (ECG) ischemic changes, complementary exams may not show any obstruction, excluding coronary occlusion as the cause of the injury.[2]

Case Report

A 42 year-old male patient, with no previous comorbidities, was admitted to a hospital in Curitiba, state of Paraná, Brazil, complaining of nonproductive cough for 6 days and odynophagia for 2 days, with symptom worsening on the previous day, including cough with yellowish sputum, dyspnea, malaise, fever, myalgia and headache. He reported recent contact with SARS-CoV-2 positive patients. On physical examination, he looked well, awake, alert, oriented, hydrated, eupneic, with a pulse of 100bpm, RR 18 breaths per minute, SpO_2 98%, temperature 36.2°C and BP 226/158mmHg. Pulmonary auscultation disclosed crackling rales in the lower third of the left hemithorax and the cardiovascular examination showed no abnormalities. BP control was achieved with Nitroglycerine and laboratory tests were requested.

On account of troponin I level at 76.1pg/mL (RV<2.3 pg/mL), an ECG was performed (Figure 1), showing sinus rhythm, STE from V1 to V3 and LV hypertrophy. The patient reported that he experienced episodes of stinging pain in left hemithorax on the previous night, lasting a few minutes.

The coronary artery angiography (figure 2) showed segmental LV dysfunction and absence of thrombi or any significant atherosclerotic process in the coronary arteries.

Keywords

Pandemics; Coronavirus-19, SARS-CoV-2, Myocarditis/complications; Electrocardiography/methods; Takotsubo Cardiomyopathy; Coronary Angiography/methods

Mailing Address: Enzo Oku Martinazzo •
Pontifícia Universidade Católica do Paraná - Rua Imac. Conceição, 1155. Postal Code 80215-901, Prado Velho, Curitiba, PR – Brazil
E-mail: enzo.martinazzoo@gmail.com
Manuscript received November 28, 2020, revised manuscript January 28, 2021, accepted February 24, 2021

DOI: https://doi.org/10.36660/abc.20201268

On day 2, in the ICU, Hydralazine, Nitrate, Amlodipine and Carvedilol were administered for Nitroglycerin weaning and BP control. The use of a nasal O_2 catheter 3L/min was required and Ceftriaxone, Azithromycin and Dexamethasone were initiated.

The CT showed pulmonary opacities, suggesting lung consolidation, air bronchogram and peripheral ground-glass opacity associated with subpleural densifications in the left lower lobe. The echocardiogram showed LV enlargement with a significant concentric hypertrophy pattern and moderate systolic dysfunction. Left atrial enlargement, mild mitral, tricuspid and aortic regurgitation and aortic root ectasia were observed.

A positive RT-PCR result for SARS-CoV-2 was obtained. Diagnostic hypotheses were raised for myocarditis associated with SARS-CoV-2, thrombosis with spontaneous lysis, microvascular injury, heart failure (HF) due to hypertensive or Takotsubo cardiomyopathy. The patient was discharged with optimized HF treatment. Upon return after 60 days, cardiac MRI (figure 3) showed: LV dilation associated with significant global systolic dysfunction (LVEF 23%), RV dilation associated with mild global systolic dysfunction (RVEF 43%), eccentric LV hypertrophy, left atrial dilation and absence of myocardial necrosis.

Discussion

In this case report, acute myocardial injury, evidenced by STE and elevated troponin, may lead to several hypothesis: the occurrence of direct myocardial injury by the virus (myocarditis). However, the MRI did not show a pattern of mesocardial fibrosis, edema or necrosis, which does not corroborate the former proposition. Because of the late diagnosis and the fact that the coronary artery angiography did not show thrombi or any atherosclerotic process, another possibility is the occurrence of thrombosis with spontaneous lysis or microvascular injury – as the hypercoagulability seen in the pro-inflammatory state in COVID-19 predisposes to acute coronary events.[1,3] Another proposition is the Takotsubo-like cardiomyopathy, which can occur in patients with SARS-CoV-2.[4] However, a cardiac ventriculography performed with coronary artery angiography and echocardiogram did not show a pattern compatible with this cardiomyopathy, which could also be excluded if the myocarditis was confirmed.[5] Finally, there is the possibility of association of some of the previous hypotheses with hypertensive cardiomyopathy, as the patient showed a hypertensive peak and probably had undiagnosed hypertension.

As for the pathophysiology of the COVID-19, there is the binding of the virus's spike protein to the ACE-

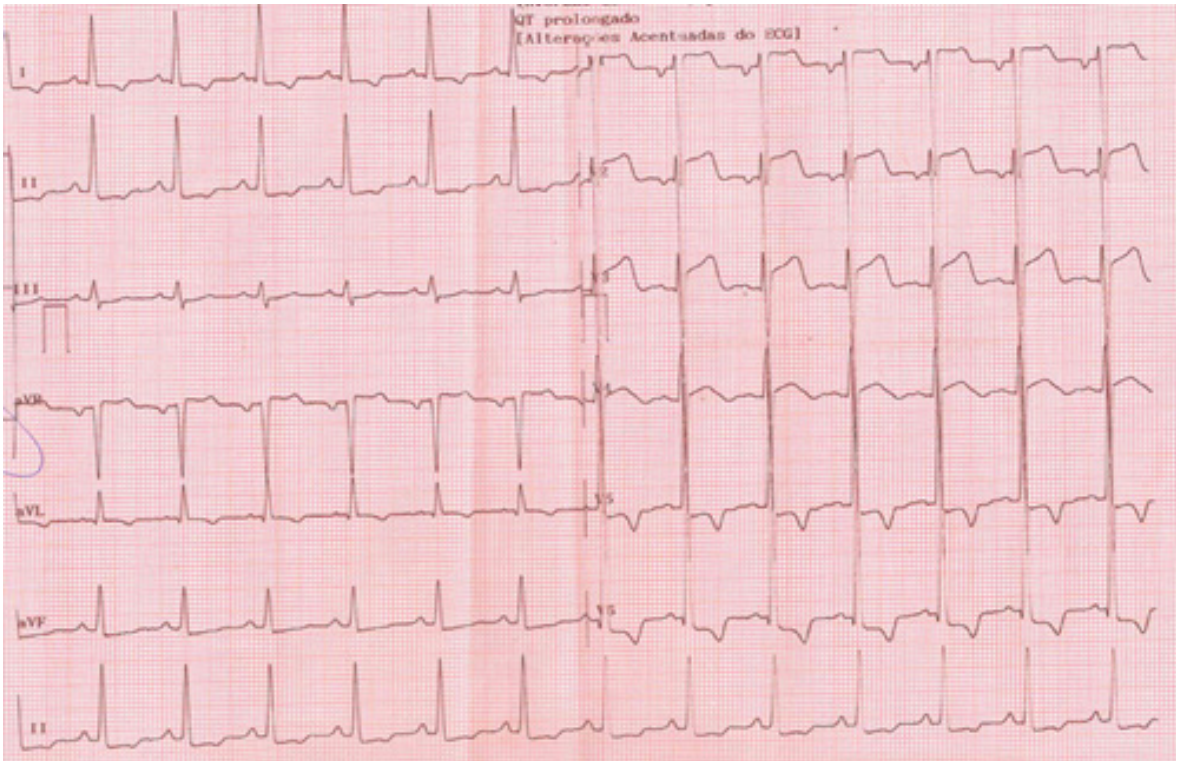


Figure 1 – *ECG performed upon admission.*

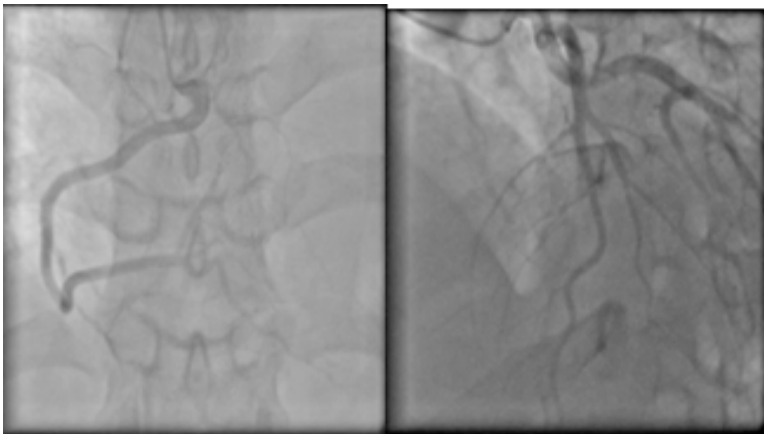


Figure 2 – *Right coronary and left anterior descending arteries coronary artery angiography.*

2 receptor, after spike activation by TMPRSS2.[3] Then, SARS-CoV-2 enters the cells through ACE-2 receptor, present in multiple body tissues, including cardiomyocytes. This enzyme converts angiotensin II, an inflammatory, vasoconstrictor, oxidative and fibrotic component, into angiotensin (1-7), with contrasting effects. Therefore, two main situations occur: the virus enters myocardial cells and, as the receptors are blocked by viral proteins, there is an increase in angiotensin II, in addition to a massive release of cytokines.[6-8]

Studies also show that acute myocardial injury can occur in COVID-19 due to myocardial ischemia or a non-ischemic process. The injury is related to more severe conditions of the disease, such as the development of HF in up to 23% of patients.[9] In China, studies suggest that up to 17% of COVID patients had elevated troponin levels.[7,8]

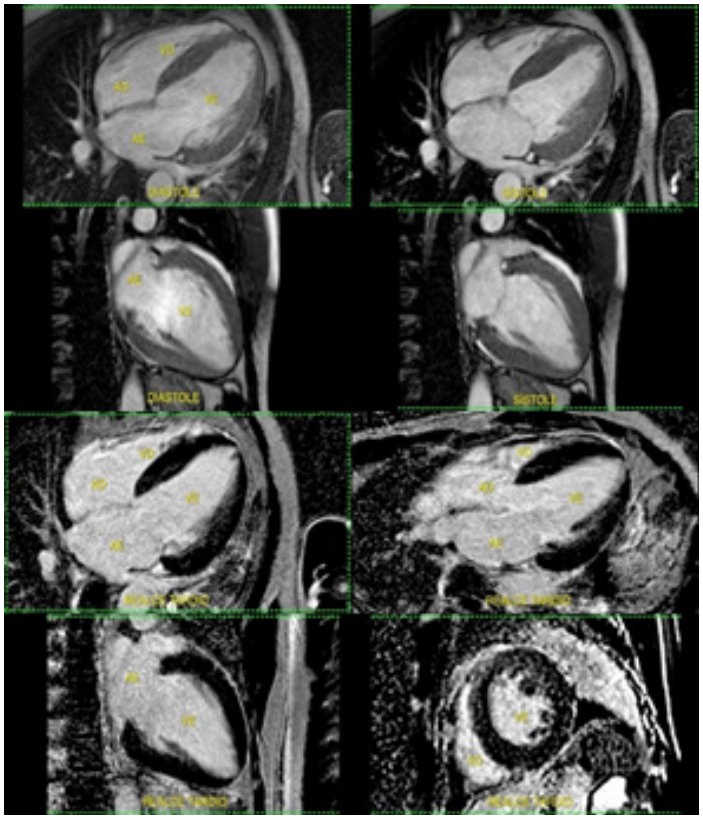


Figure 3 – *Dynamic contrast-enhanced MRI (top) and delayed enhancement (bottom).*

Troponin elevation in non-ischemic myocardial injury can be explained by tissue hypoxia, sepsis, systemic inflammatory response, venous thromboembolism and myocardial stress.[8] If there is an obstruction, the hypothesis is that the virus may cause instability and intraplaque hemorrhage, exposing collagen, causing microvascular injury and thrombus formation.[1,3,8] In the absence of the atherosclerotic process, it is possible that the imbalance between oxygen supply and demand results in a type 2 acute myocardial infarction.[3] In addition to the direct myocardial injury mechanisms, there are indirect mechanisms: cytokine storm and Takotsubo. This cardiomyopathy represents almost 3% of acute coronary syndrome suspicions and it is known that conditions such as respiratory infection, emotional and physical stress can be triggers, leading to transient LV dysfunction.[3,5,7]

Compared with similar cases (Table 1), Aragão et al.[2] described a troponin elevation, but it differs from our patient due to the absence of HF, verified by the significant reduction in the left ventricular ejection fraction (LVEF). Inciardi et al.[10] also described an LVEF reduction; however, it was milder. Huyut,[11] on the other hand, did not show an increase in troponin; however, the transient reduction in LVEF suggests cardiomyopathy.[11]

Stefanini et al.[12] demonstrated that 85.7% of patients in a case series had signs of infarction with STE as the first symptomatic manifestation of COVID-19 and that 39.3% did not have any evidence of obstructive disease. Our patient had STE, but it was not the first manifestation, in addition to not showing occlusion in the coronary artery angiography. Like most of their patients, ours followed a benign pattern.[12]

Conclusion

This case report described an atypical case of cardiac manifestation of COVID-19, in which there was STE without evidence of coronary disease, progressing to HF with reduced ejection fraction. As previously discussed, the hypotheses of viral myocarditis, thrombosis with spontaneous lysis, microvascular injury, Takotsubo and hypertensive cardiomyopathies have not been fully established, and may even coexist. Finally, we emphasize that the elucidation of the involved mechanisms contributes to the earlier identification and adequate management of patients, leading to better outcomes and understanding of possible sequelae.

Author Contributions

Conception and design of the research: Martinazzo EO; Acquisition of data; Analysis and interpretation of the data; Writing of the manuscript and Critical revision of the

Table 1 – Case Comparison

Cases	Curitiba	Aragão et al.[2]	Inciardi et al.[10]	Huyut[11]
Age/gender	42/male	39/male	53/female	59/female
LVEF	23%	62%	40%	52%
Troponin I	76.1pg/mL	25.20ng/mL	0.89*	Normal
ECG	STE	STE	STE	Normal
RT-PCR SARS-CoV-2	Positive	Positive	Positive	Positive
Hypokinesis	Diffuse	Mid-cavity anteroseptal segment	Diffuse	-

**High-sensitivity cardiac troponin-T. LVEF: left ventricular ejection fraction; ECG: electrocardiogram.*

manuscript for intellectual content: Ragonetti C, Martinazzo EO, Fazionato FM, Ferreira GOG, Santana MP, Hartmann C.

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 Pontifícia Universidade Católica do Paraná under the protocol number 30188020.7.1001.0020. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

References

1. Schiavone M, Gobbi C, Biondi-Zoccai G,D'SAscenzo F, Palazzioli A, Gasparetti A, et al. Acute coronary syndromes and Covid-19: exploring the uncertainties. J Clin Med. 2020 Jun; 9(6):1683.
2. Aragão RC de A, Alves MC, Passos HD, Gonçalves FG, Baumworcel L, Barreto Filho JA. Lesão miocárdica na Covid-19: um desafio para o cardiologista clínico. Arq Bras Cardiol. 2020; 115(1):139-41.
3. Albuquerque J, Neto DF, Marcondes-Braga FG, Figueiredo Neto JA,Marcondes-Braga,F, Moura LZ,Figueiredo ALS, et al. Coronavirus e o miocardio:revisão. Arq Bras Cardiol.2020;114(6):1051-7;
4. Singh S, Desai R, Gandhi Z,Fong HK, Dores Wamy S, Desai V. et al. Takotsubo syndrome in patients with Covid-19: a systematic review of published cases. SN Compr Clin Med. 2020; 2(11):2102-8.
5. Ghadri J, Wittstein IS, Prasad A ,Sharkey S, Dote K, Akashi YJ, et al. International expert consensus document on Takotsubo syndrome (part I): clinical characteristics, diagnostic criteria, and pathophysiology. Eur Heart J. 2018; 39(22):2032-46.
6. Çınar T, Hayıroğlu Mİ, Çiçek V,Uzun M, Orhan AL. Covid-19 and acute myocarditis: current literature review and diagnostic challenges. Rev Assoc Med Bras. 2020; 66 2(Suppl 2):48-54.
7. Siripanthong B, Nazarian S, Muser D, Deor R, Santangeli P, Khanji M, et al. Recognizing Covid-19–related myocarditis: the possible pathophysiology and proposed guideline for diagnosis and management. Heart Rhythm. 2020; 17(9):1463-71.
8. Imazio M, Klingel K, Kindermann I, Brucato A, Rosa FG, Adler Y, et al. Covid-19 pandemic and troponin: indirect myocardial injury, myocardial inflammation or myocarditis? Heart. 2020 Aug 1; 106(15):1127-31. [Internet] Disponível em: http://heart.bmj.com/content/106/15/1127.abstract.
9. Driggin E, Madhavan MV, Bikdeli B,CHuich T, Laracy J, Biondi-Zoccai G, et al. et al. Cardiovascular considerations for patients, health care workers, and health systems during the Covid-19 pandemic. J Am Coll Cardiol. 2020; 75(18):2352-71.
10. Inciardi RM, Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, et al. Cardiac involvement in a patient with coronavirus disease 2019 (Covid-19). JAMA Cardiol. 2020; 5(7):819-24.
11. Huyut MA. Nova pneumonia por coronavírus e miocardiopatia: relato de caso. Arq Bras Cardiol. 2020; 114(5):843-5.
12. Stefanini GG, Montorfano M, Trabattoni D,Andreini D, Ferrante G, Ancona M, et al. ST-Elevation myocardial infarction in patients with Covid-19: clinical and angiographic outcomes. Circulation. 2020;141(25); 2113-6.

Cardiovascular Imaging in COVID-19

Rujittika Mungmungpuntitpantip[1] *and Viroj Wiwanitkit*[1]
Dr. DY Patil University,[1] *Pune – India*

Dear Editor,

We would like to share ideas on the publication "Cardiovascular Imaging in Patients with COVID-19."[1] Grossman and Lima concluded that "nuclear cardiologists and nuclear medicine physicians must be aware of incidental findings in asymptomatic patients with COVID-19, and they should optimize MPI protocols, when the procedure is necessary."[1] The results in this study are concordant with a previous report from Asia.[2] Imaging can help identify both heart and lung problems that might asymptomatically occur due to COVID-19 or a previous silent pathology.[2] An important point is the differential diagnosis of the new lesion and the previous underlying pathology. In tropical countries, there might be a common pathology, such as tuberculosis, that results in difficulty in interpreting new heart and lung problems due to COVID-19.[3] Since image interpretation depends mainly on the radiologist, it is necessary for radiologists to increase awareness and concern when interpreting clinical images during the COVID-19 pandemic.

Keywords

Cardiovascular Diseases; Lung Diseases; Coronavirus, COVID-19; Pandemics; Diagnostic Imaging; Asymptomatic Patients

Mailing Address: Rujittika Mungmungpuntitpantip •
Private Academic Consultant, Bangkok Thailand bangkok 1039 - Thailand
E-mail: rujittika@gmail.com
Manuscript received December 22, 2020, revised February 10, 2021, accepted February 10, 2021

DOI: https://doi.org/10.36660/abc.20201356

References

1. Grossman GB, Lima RL. Cardiovascular Imaging in Patients with COVID-19. Arq Bras Cardiol. 2020 Nov;115(5):973-4.
2. Attavirayanuparuktham B. Abnormal heart imaging in COVID-19 patients: a note. Adv Lab Med Int. 2020;10:18-9.
3. Yasri S, Wiwanitkit V. Tuberculosis and novel Wuhan coronavirus infection: Pathological interrelationship. Indian J Tuberc. 2020 Apr;67(2):264.

Prevalence of Systemic Arterial Hypertension and Diabetes Mellitus in Individuals with COVID-19: A Retrospective Study of Deaths in Pernambuco, Brazil

Lucas Gomes Santos,[1] Jussara Almeida de Oliveira Baggio,[1] Thiago Cavalcanti Leal,[1] Francisco A. Costa,[1] Tânia Rita Moreno de Oliveira Fernandes,[2] Regicley Vieira da Silva,[1] Anderson Armstrong,[2] Rodrigo Feliciano Carmo,[2] Carlos Dornels Freire de Souza[1]

Universidade Federal de Alagoas - Curso de Medicina,[1] Maceió, AL - Brazil

Universidade Federal do Vale do São Francisco – Medicina,[2] Petrolina, PE - Brazil

Introduction

In December 2019, health authorities in Hubei province, in the People's Republic of China, identified and reported to the World Health Organization (WHO) an outbreak of pneumonia with an unknown etiological agent.[1] In early January, the SARS-CoV-2 virus (Severe Acute Respiratory Syndrome Coronavirus 2) was identified and the disease was called COVID-19 (Coronavirus Disease 2019).[2]

On August 4, 2020, the disease has infected 18,316,072 people and caused the death of 694,715. The USA, Brazil and India occupy the first positions in number of infected people.[3] In Brazil, the first case was confirmed on February 26th in the city of São Paulo. Between the first case and August 4, 2020, the country had 2,750,249 people infected and 94,665 deaths.[4]

Due to the global impact caused by the pandemic, there is an urgent need to produce knowledge about the new coronavirus. The characterization of infected people is essential for tackling the disease and for economic recovery. Since the beginning of the pandemic, several studies have been published for this purpose, and have shown that the disease affects more severely elderly people with comorbidities.[5,6] Systemic arterial hypertension (SAH) and diabetes mellitus (DM) are the most frequent comorbidities in people who have died, and their pathophysiology seems to favor the development of more severe conditions.[7-9]

COVID-19 is still expanding in Brazil and, because of that, it is important to understand the characteristics of infected people in the country and also in different states, due to Brazil's continental size and socioeconomic differences.[10] The state of Pernambuco was particularly affected, with a record of 98,833 cases and 6,717 deaths by August 4, 2020.[11]

This study aimed to describe the prevalence and the clinical and epidemiological profile of deaths from COVID-19 in Pernambuco between March 12 and May 14, 2020, among people that had SAH and/or DM as previous diseases.

Methods

This is a cross-sectional observational study involving all deaths from COVID-19 reported in Pernambuco, between March 12 and May 14, 2020, of people that had SAH and DM as previous diseases. We analyzed the following variables: sex, age group, time between the onset of the first symptoms and death, signs/symptoms, the number and type of associated comorbidities, in addition to SAH and DM and lifestyle habits (smoking and alcoholism). The data were obtained from the monitoring page of COVID-19 in the state of Pernambuco (https://dados.seplag.pe.gov.br/apps/corona.html) on May 15, 2020. After data collection, we made some adjustments in the database, which consisted of adjustment of signs/symptoms and comorbidities and exclusion of inconsistent records. For statistical analysis, categorical variables were initially described by frequencies (absolute and relative) and continuous variables by measures of central tendency and dispersion. The Mann-Whitney test was used to compare the time between symptom onset and death between females and males and the Kruskal-Wallis test was used to compare the age groups and comorbidities with the subsequent application of a post-hoc test. We adopted a confidence interval of 95% and a significance level of 5%. The analyses were performed with SPSS software version 24.0 (IBM Corporation). This study used public domain data, in which it is not possible to identify individuals. For this reason, approval by the Research Ethics Committee was not necessary.

Results

Until May 14, there were 1,461 deaths in the state of Pernambuco according to the database analyzed. We excluded 185 cases due to low-quality data (absence and/or inconsistency among the variables), resulting in 1,276 deaths. According to the records, 338 (26.48%) had SAH and 252 (19.74%) had DM as previous diseases: 158 (12.4%) had only SAH, 72 (5.6%) only DM and 180 (14.1%) had SAH + DM. 53.3% of the individuals with SAH had DM and 71.4% of diabetics had SAH.

Keywords

Coronavirus-19; SARS-CoV-19; Pandemics; Hypertension/complications; Diabetes Mellitus/complications; Risk Factors/prevention and control; Aged; Prevalence.

Mailing Address: Carlos Dornels Freire de Souzaa •
Universidade Federal de Alagoas - Campus Arapiraca - Medicina
Av. Manoel Severino Barbosa, s/n. Postal Code 57309-005, Arapiraca, AL – Brazil
E-mail: carlos.freire@arapiraca.ufal.br
Manuscript received June 05, 2020, revised manuscript October 23, 2020, accepted November 11, 2020

DOI: https://doi.org/10.36660/abc.20200885

Brief Communication

SAH people died from COVID-19 in 56 cities, including Recife (n=141), Jaboatão dos Guararapes (n=27), Paulista (n=27) and Olinda (n=17), totaling 62.72% (n=212) of deaths in the state. People with DM died from COVID-19 in 49 cities, including Recife (n=104), Jaboatão dos Guararapes (n=21), Olinda (n=13), Cabo de Santo Agostinho (n=12) and Paulista (n=12), in the metropolitan region of Recife. These four cities accounted for 64.28% (n=162) of all deaths.

The median (in days) time between the onset of signs/symptoms and death was 8.0 (IIQ 9.0), with no significant difference between groups of comorbidities (p=0.633), sex (p=0.364), age group (p=0.111) and in the comparison between elderly and non-elderly individuals (p=0.257) (Figure 1). The clinical epidemiological profile showed a homogeneous distribution between sexes in the general group (n=410). However, the disaggregated analysis showed a higher prevalence of DM and SAH in the male population (DM — 61.3% were men and 38.9% women; SAH — 53.2% were men and 46.8%, women). On the other hand, considering only individuals with both comorbidities, there was a predominance of women (53.3%) (Table 1).

The proportion of elderly people in the studied population also stood out (73.4% were 60 years old or older; n=301). Of these, 85.7% (n=258) had SAH, 59.5% (n=179) DM and 45.2% (n=136) had the two comorbidities. The most frequent signs/symptoms were dyspnea (74.1%; n=304), cough (72.2%; n=296), fever (68.5%; n=281) and O_2 saturation <95% (66.1%; n=271) (Table 1).

Regarding comorbidities/associated risk factors, it was observed that 73.3% (n=100) of hypertensive patients and 54.2% (n=39) of diabetics had other comorbidities/associated risk factors. In the group with SAH + DM, this percentage was 54.4% (n=141). The most frequent comorbidities were: heart disease (19.5%/n=80), obesity (8.3%; n=34), previous respiratory disease (7.3%; n=30) and nephropathy (7.8%; n=32). The prevalence of smoking (current or previous) was 8.8% (n=36) and alcoholism (current or previous), 3.4% (n=14) (Table 1).

Discussion

The majority of deaths described in the present study is concentrated in larger cities (Recife and Jaboatão dos Guararapes) and may be related to the number of individuals exposed to SARS-CoV-2 virus and the high number of people moving around, since these are the two most populous cities in the state. Added to this, the deaths can also be explained by age composition and the high prevalence of chronic non-communicable diseases.[12] The dissemination of COVID-19 in Pernambuco seems to follow the pattern of other countries: from large urban centers, it spreads to medium and small cities.[13]

The deaths occurred mainly among people older than 60, especially from 70 to 79, which is similar to other countries previously affected by the pandemic.[7,8] The profile of comorbidities in the Brazilian population is also a factor to be taken into account. The prevalence of DM is 9.4% in the

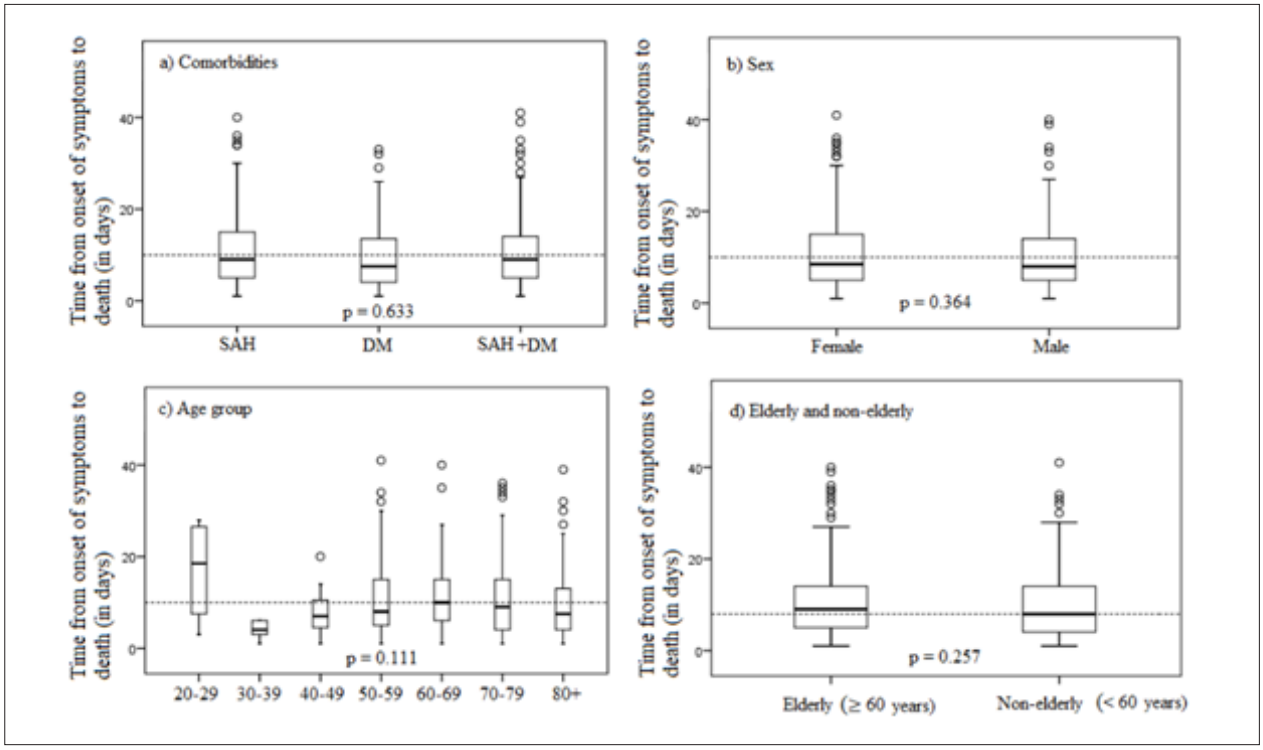


Figure 1 – *Boxplot from the onset of first symptoms and death of individuals with COVID-19 and systemic arterial hypertension and/or diabetes in Pernambuco, Brazil. SAH: Systemic arterial hypertension; DM: Diabetes mellitus.*

Table 1 – Clinical epidemiological characterization of deaths from COVID-19 with systemic arterial hypertension and diabetes mellitus as previous diseases, in Pernambuco, Brazil.

Variable	SAH (n=158)		DM (n=72)		SAH + DM (n=180)		Total (n= 410)	
Sex	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Female	74	46.8	28	38.9	96	53.3	198	48.3
Male	84	53.2	44	61.1	84	46.7	212	51.7
Age[1]								
20–29	1	0.6	2	2.8	1	0.6	4	1.0
30–39	2	1.3	1	1.4	2	1.1	5	1.2
40–49	9	5.7	4	5.6	10	5.6	23	5.6
50–59	24	15.2	22	30.6	31	17.2	77	18.8
60–69	40	25.3	13	18.1	41	22.8	94	22.9
70–79	38	24.1	22	30.6	55	30.6	115	28.0
80+	44	27.8	8	11.1	40	22.2	92	22.4
Signs/symptoms[2]								
Dyspnea	111	70.3	54	75.0	139	77.2	304	74.1
Cough	117	74.1	51	70.8	128	71.1	296	72.2
Fever	110	69.6	46	63.9	125	69.4	281	68.5
O2 saturation <95%	99	62.7	57	79.2	115	63.9	271	66.1
Sore throat	13	8.2	12	16.7	17	9.4	42	10.2
Diarrhea	6	3.8	4	5.6	11	6.1	21	5.1
Vomit	4	2.5	5	6.9	6	3.3	15	3.7
Myalgia	5	3.2	0	0.0	8	4.4	13	3.2
Asthenia	6	3.7	1	1.4	4	2.2	11	2.7
Number of Comorbidities behind SAH and DM								
One comorbidity	58	36.7	33	45.8	0	0.0	91	22.2
Two comorbidities	68	43.0	28	38.9	82	45.6	178	43.4
Three or more	32	20.3	11	15.3	98	54.4	141	34.4
Comorbidities								
Cardiopathy	25	15.8	19	26.4	36	20.0	80	19.5
Obesity	14	8.9	5	6.9	15	8.3	34	8.3
Previous respiratory disease	16	10.1	3	4.2	11	6.1	30	7.3
Nephropathy	14	8.9	3	4.2	15	8.3	32	7.8
Previous neurological disease	13	8.2	6	8.3	8	4.4	27	6.6
Cancer	5	3.2	1	1.4	6	3.3	12	2.9
Lifestyle Habits								
Current smoking	12	7.6	3	4.2	8	4.4	23	5.6
Previous smoking	7	4.4	2	2.8	4	2.2	13	3.2
Current alcohol consumption	5	3.2	2	2.8	4	2.2	11	2.7
Previous alcohol consumption	2	1.3	0	0.0	1	0.6	3	0.7

[1]No records of individuals under 20. [2] Signs/symptoms and comorbidities with frequency <2.0% were suppressed. SAH: Systemic arterial hypertension; DM: Diabetes mellitus.

general population and is even more significant with increasing age, whose prevalence is 22.6% in the population older than 60.[14] The prevalence of SAH is around 24.0%, and 60.9% in the elderly population.[15] Individuals with SAH and DM are more likely to develop severe cases of COVID-19 and sometimes it is fatal.[16]

In addition to age, sex is another relevant feature. In a review by Li et al.,[17] in China, about 60% of people infected with SARS-CoV-2 were men. Similar results were presented by Zhou et al.,[8] both in survivors (59% were men) and in individuals who died (70% men), a higher percentage of men. The relationship between sex and COVID-19 is still unclear, but the worst outcome in males may be related to the greater number of comorbidities present in men or an immune system response different from that observed in the female population.[17]

The time between the onset of symptoms and death was shorter than that previously described in the literature (18.5 days).[6] In Brazil, the presence of cardiovascular comorbidities can reduce lifespan by up to four days.[18] However, the findings of our study may be underestimated, as it is necessary to consider a potential difficulty in recognizing the first symptoms, especially in individuals with precarious socioeconomic conditions and low educational level. In addition, memory bias is a limitation of this variable.

In Pernambuco, 43.9% of the deceased individuals investigated had SAH and DM simultaneously. In a study carried out in New York City involving hospitalized patients, the most frequent comorbidities were SAH (56.6%), obesity (41.7%) and DM (33.8%), respectively.[7] These comorbidities have also been described as the most frequent ones in different investigations.[8,19,20] The prevalence of these diseases varied between countries: in China, for example, the presence of these diseases is lower than that observed in countries like Italy and the USA.[21]

So far, it is known that the SARS-CoV-2 virus binds to the angiotensin-converting enzyme 2 (ACE-2), decreasing the activity of this type of receptor, increasing vascular permeability.[22] This receptor has a greater expression in the lungs and heart, being fundamental for the functioning of these systems.[23] In patients with SAH and DM, there is an increase in this type of receptor compared to the healthy population, which may lead to the development of more severe diseases.[23] Furthermore, SARS-CoV-2 promotes endothelial damage mainly in the pulmonary capillaries, promoting a pro-coagulation state, inflammatory vascular state and cell infiltrate, which may justify more severe conditions in patients with DM and obese people.[24-26]

Additionally, individuals with DM appear to have a response to SARS-CoV-2 with large volumes of interferon (IFN) and a late Th1/Th17 response contributing to a more intense inflammatory response.[27] A recent in vitro study demonstrated that the concentration of glucose in monocytes was related to increased viral replication and production of pro-inflammatory cytokines.[28]

The sum of different comorbidities in the same individual may result in amplification of inflammatory response and favor the rapid progression and/or worsening of the clinical condition, reducing patient survival.[27,28] In this analysis, the most prevalent comorbidities associated with DM and SAH were unspecified heart disease and obesity. These comorbidities were also observed in the New York study, in which 18.0% of the individuals had heart disease and 41.7% were obese.[5] Currently, the high prevalence of obesity has been a serious public health problem in most countries, including Brazil.

Lifestyle habits, such as smoking and excessive alcohol consumption, may also aggravate COVID-19. When infected, smokers are 3.5 times more likely to develop aggressive forms of the disease than non-smokers.[29] Therefore, smoking increases the risk of lung injury culminating in chronic respiratory bronchiolitis, various types of pneumonia, cancer and pulmonary emphysema,[30] which, individually, are risk factors for SARS-CoV-2 and, together, decrease lung function, increasing virus susceptibility.

Chronic consumption of alcoholic beverages results in increased pro-inflammatory response and reduced anti-inflammatory defenses mediated by cytokines.[31] Associated to this, the immune system is impaired because it reduces the ability to fight against infectious agents through innate and adaptive immunity, exposing those infected by SARS-CoV-2 to a more aggressive forms of the disease.[31]

The cumulative effects of comorbidities on aggravation and mortality by COVID-19 is unknown. It is possible that the sum of comorbidities may act together to facilitate both the cellular entry of SARS-CoV-2 mediated by ACE-2[26] into the cells and favor more aggressive inflammatory responses. Studies on this aspect are strongly recommended.

Even with all the methodological precautions adopted, this study has limitations: i. The database used is in the public domain and was built from the COVID-19 notification forms, without adequate standardization of variables and lack of detailed information (glycemic levels, obesity stage, pressure control, among others); ii. Throughout the pandemic, different notification forms were implemented, excluding and/or adding variables; and iii. As it is a new disease, without a clear list of signs/symptoms, it is likely that the less common ones were not identified by patients and registered, especially at the beginning of the pandemic.

Conclusion

The prevalence of SAH was higher than the prevalence of DM in individuals who died from COVID-19. In the elderly, the prevalence was higher than that observed in non-elderly individuals. In addition, there was an important accumulation of comorbidities and risk factors. The clinical epidemiological profile was characterized by elderly people, signs/symptoms indicative of respiratory impairment and predominance of more than one comorbidity. There was no difference between the time of onset of the first symptoms and death in the analysis according to sex and age group.

We recommend studies that can estimate the risk of severity according to the number and type of pre-existing comorbidities.

Author Contributions

Conception and design of the research; Acquisition of data; Analysis and interpretation of the data; Statistical analysis; Obtaining financing; Writing of the manuscript; Critical revision of the manuscript for intellectual content: Santos LG, Baggio JAO, Leal TC, Costa FA, Fernandes TRMO, Silva RV, Armstrong A, Carmo RF, Souza CDF

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. Shereen MA, Khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J AdvancRes [Internet]. 2020 Mar 16 [cited 2020 Jun 2];24:91-98. DOI doi.org/10.1016/j.jare.2020.03.005. Available from: https://www.sciencedirect.com/science/article/pii/S2090123220300540.
2. Strabelli TMV, Uip DE. COVID-19 e o Coração. Arq Bras Cardiol. [Internet]. 2020 Mar 30 [cited 2020 Jun 2];114(4):598-600. DOI 10.36660/abc.20200209. Available from: https://www.scielo.br/scielo.php?script=sci_arttext&pid=S0066-782X2020000400598&lng=pt&nrm=iso
3. Organização Mundial da Saúde. OMS.Coronavirus disease (COVID-19) outbreak situation [Internet]. 2020 [cited 2020 Aug 04]. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019?gclid=CjwKCAjwlZf3BRABEiwA8Q0qq-0YAuqVKv-pzn_skILWYn5zVY7lsveG_GHw06SzO6rGcXqRkSJZGRoC4_8QAvD_BwE.
4. MonitoraCOVID-19. Painel Brasil [Internet]. 2020 [cited 2020 Jun 10]. Available from: https://bigdata-covid19.icict.fiocruz.br/.
5. Porcheddu R, Serra C, Kelvin D, Kelvin N, Rubino S. Similarity in Case Fatality Rates (CFR) of COVID-19/SARS-COV-2 in Italy and China. J Infect Dev Ctries .[Internet]. 2020[cited 2020 Jun 10];14(2):125–128. Available from: https://jidc.org/index.php/journal/article/view/32146445.
6. Shereen M A, Suliman K, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res [Internet]. 2020 Jul [cited 2020 Jul 10];24:91-98. Available from: https://www.sciencedirect.com/science/article/pii/S2090123220300540.
7. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area. JAMA [Internet]. 2020 May 26 [cited 2020 Jun 8];323(20):2052-2059. Available from: https://jamanetwork.com/journals/jama/fullarticle/2765184.
8. 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 [Internet]. 2020 Mar 28 [cited 2020 Jun 2];395(10229):1054–1062. Available from: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30566-3/fulltext.
9. Teuwen L-A, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. Nat Rev Immunol [Internet]. 2020 May 21 [cited 2020 Jun 14];1–3. Available from: http://www.nature.com/articles/s41577-020-0343-0
10. Marson F A L, Ortega M M. COVID-19 in Brazil. Pulmonology [Internet]. 2020 Jul/Aug [cited 2020 Jul 2];26:241-4. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7183991/
11. Pernambuco(Estado). Secretaria de Saúde. Centro de Informações Estratégicas de Vigilância em Saúde. Informe Epidemiológico Nº 156/2020 – Pernambuco. 04 de agosto de 2020. Pernambuco (PE); 2020. [cited 2020 Aug 04]. Available from: https://12ad4c92-89c7-4218-9e11-0ee136fa4b92.filesusr.com/ugd/3293a8_965059e30c594eac88e6b4f872b6c042.pdf
12. Melo SPDC, Cesse EAP, Lira PIC, Rissin A, Cruz RSBLC, Filho MB. Doenças crônicas não transmissíveis e fatores associados em adultos numa área urbana de pobreza do nordeste brasileiro. Cien Saude Colet. 2019;24(8):3159-3168.
13. Carmo RF, Nunes BEBR, Machado MF, Armstrong AC, Souza CDF. Expansion of COVID-19 within Brazil: the importance of highways.J Travel Med.2020;0820.
14. Malta DC, Duncan BB, Schmidt MI, Machado MI, Silva AG, Bernal RTI, et al. Prevalência de diabetes mellitus determinada pela hemoglobina glicada na população adulta brasileira, Pesquisa Nacional de Saúde. Rev Bras Epidemiol [Internet]. 2019 [cited 2020 Jun 21];22(27):1-13. Available from: https://www.scielo.br/scielo.php?pid=S1415-790X2019000300408&script=sci_arttext&tlng=pt.
15. Brasil. Ministério da Saúde. Vigitel Brasil 2018: vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico: estimativas sobre frequência e distribuição sociodemográfica de fatores de risco e proteção para doenças crônicas nas capitais dos 26 estados brasileiros e no Distrito Federal em 2018. Ministério da Saúde, Brasília; 2019.
16. Cuschieri S, Grech S. COVID-19 and diabetes: The why, the what and the how. J Diabetes Complications. 2020 Sep; 34(9): 107637.
17. Li L, Huang T, Wang Y, Wang Z, Liang Y, Huang T, et al. COVID-19 patients' clinical characteristics, discharge rate, and fatality rate of meta-analysis. J Med Virol [Internet]. 2020 Jun 23 [cited 2020 Jul 11];92(6):577–83. Available from: https://pubmed.ncbi.nlm.nih.gov/32162702/.
18. Souza CDF, Leal TC, Santos LG. Does Existence of Prior Circulatory System Diseases Accelerate Mortality Due to COVID-19? Arq Bras Cardiol [Internet]. 2020 Mai 21 [cited 2020 Jul 24]; 115(1):146-147Available from: http://publicacoes.cardiol.br/portal/abc/portugues/2020/v11501/pdf/11501026.pdf
19. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med [Internet]. 2020[cited 2020 Jun 6]; 382:727-733. Available from: https://www.nejm.org/doi/full/10.1056/nejmoa2001017.
20. Adhikari SP, Meng S, Wu Y, Mao Y, Ye E, Wang Q, et al. Epidemiology, Causes, Clinical Manifestation and Diagnosis, Prevention and Control of Coronavirus Disease (COVID-19) During the Early Outbreak Period: A Scoping Review. Infect Dis Poverty .[Internet]. 2020[cited 2020 Jun 2]; 9(1):1-12. Available from: https://link.springer.com/article/10.1186/s40249-020-00646-x.
21. Ejaz H, Alsrhani A, Zafar A, Javed H, Junaid K Abdalla AE, et al. COVID-19 and comorbidities: Deleterious impact on infected patients. J. Infect. Public Health. 2020 [Internet]. 2020[cited 2020 out 23]; 9(1):1-12. Available from: https://www.sciencedirect.com/science/article/pii/S1876034120305943#bib0065

22. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. Cell .[Internet]. 2020 Apr 16[cited 2020 Jun 6];181(2):271-280.e8. Available from: https://www.sciencedirect.com/science/article/pii/S0092867420302294.

23. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol. [Internet]. 2020[cited 2020 Jul 1]; 17: 259–260. Available from: https://www.nature.com/articles/s41569-020-0360-5.

24. Teuwen L-A, Geldhof V, Pasut A, Carmeliet P. COVID-19: the vasculature unleashed. Nat Rev Immunol. [Internet]. 2020 May 21 [cited 2020 Jun 14];1–3. Available from: http://www.nature.com/articles/s41577-020-0343-0

25. Kaur R, Kaur M, Singh J. Endothelial dysfunction and platelet hyperactivity in type 2 diabetes mellitus: Molecular insights and therapeutic strategies. Cardiovasc Diabetol. [Internet]. 2018 Aug 31[cited 2020 Jul 1];17(1):121. Available from: https://pubmed.ncbi.nlm.nih.gov/30170601/.

26. Engin A. Endothelial dysfunction in obesity. In: Advances in Experimental Medicine and Biology. Adv Exp Med Biol. [Internet]. 2017[cited 2020 Jul 4]; 960: 345–79. . Available from: https://pubmed.ncbi.nlm.nih.gov/28585207/.

27. Codo AC, Davanzo GG, Monteiro LB, Souza G, Muraro S, Carregari V, et al. Elevated Glucose Levels Favor Sars-Cov-2 Infection and Monocyte Response Through a Hif-1α/Glycolysis Dependent Axis. SSRN [Internet]. 2020[cited 2020 Jul 8]; 1-32. Available from: https://www.unicamp.br/unicamp/sites/default/files/2020-05/SSRN-id3606770_Cell%20Met.pdf.

28. Muniyappa R, Gubbi S. COVID-19 pandemic, coronaviruses, and diabetes mellitus. Am J Physiol Endocrinol Metab. [Internet]. 2020 [cited 2020 Jul 12]; 318:736-741. Available from: https://www.unicamp.br/unicamp/sites/default/files/2020-05/SSRN-id3606770_Cell%20Met.pdf.

29. Guan W, Ni Z, Hu Y, Liang W, Ou C, He J, et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J M. [Internet] 2020 [cited 2020 Aug 04]; 382:1708-1720. Available from: https://pubmed.ncbi.nlm.nih.gov/32109013/

30. U.S. Department of Health and Human Services. The health consequences of smoking: 50 years of progress. A report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services; 2014[cited 2020 Aug 04]. Available from: https://www.cdc.gov/tobacco/data_statistics/sgr/50th-anniversary/index.htm

31. Testino G. Are Patients With Alcohol Use Disorders at Increased Risk for Covid-19 Infection? Alcohol Alcohol. 2020 [cited 2020 Aug 04]; 55(4):344-6. Available from: https: //academic.oup.com/alcalc/advance-article/doi/10.1093/alcalc/agaa037/5827422

Erratum

May 2019 Issue, vol. 112 (5), pages 649-705

In the "Updated Geriatric Cardiology Guidelines of the Brazilian Society of Cardiology – 2019", with DOI: https://doi.org/10.5935/abc.20190086, published in the journal Arquivos Brasileiros de Cardiologia, the name of the author Felipe Costa Fuchs was included on page 649, in the authors of chapter 6; on page 650, in the update authors; and on page 652, in the declaration of potential conflict of interest.

May 2020 Issue, vol. 114 (5), pages 943-987

In the English version of the "Updated Geriatric Cardiology Guidelines of the Brazilian Society of Cardiology – 2019", with DOI: https://doi.org/10.36660/abc.20200407, published in the journal Arquivos Brasileiros de Cardiologia, 114(5):943-987, correct the value "50–85%" in line 4, column 2, to "50–80%", according to the Portuguese version of the document.

DOI: https://doi.org/10.36660/abc.20210642