INTERNATIONAL JOURNAL OF

Cardiovascular SCIENCES

MEET WOMEN WHERE THEY ARE TO PROVIDE BETTER CARDIOVASCULAR CARE

Guest Editors: Dr. Glaucia Moraes and Dr. Roxana Mehran

Volume 34 - Number 4 | July / August | ISSN 2359-4802 | ISSN online 2359-5647

INTERNATIONAL JOURNAL OF

Cardiovascular SCIENCES

ISSN 2359-4802 / IJCS ONLINE: ISSN 2359-5647

Exterior

Amalia Peix - Instituto de Cardiología y Cirugía Cardiovascular, Havana – Cuba
Amelia Jiménez-Heffernan - Hospital Juan Ramón Jiménez, Huelva – Spain
Ana Isabel Venâncio Oliveira Galrinho - Hospital Santa Marta, Lisboa – Portugal
Ana Maria Ferreira Neves Abreu - Hospital Santa Marta, Lisboa – Portugal
Ana Teresa Timóteo - Hospital Santa Marta, Lisboa – Portugal
Charalampos Tsoumpas - University of Leeds, Leeds – England
Chetal Patel - All India Institute of Medical Sciences, Delhi – Indian
Edgardo Escobar - Universidad de Chile, Santiago – Chile
Enrique Estrada-Lobato - International Atomic Energy Agency, Vienna – Austria
Erick Alexanderson - Instituto Nacional de Cardiología - Ignacio Chávez, Ciudad de México – México
Fausto Pinto - Universidade de Lisboa, Lisboa - Portugal
Ganesan Karthikeyan - All India Institute of Medical Sciences, Delhi – Indian
Guilherme Vianna e Silva - Texas Heart Institute, Texas – USA
Horacio José Faella - Hospital de Pediatría S.A.M.I.C. "Prof. Dr. Juan P. Garrahan", Caba – Argentina
James A. Lang - Des Moines University, Des Moines – USA
James P. Fisher - University of Birmingham, Birmingham – England
João Augusto Costa Lima - Johns Hopkins Medicine, Baltimore – USA
Jorge Ferreira - Hospital de Santa Cruz, Carnaxide, Portugal
Manuel de Jesus Antunes - Centro Hospitalar de Coimbra, Coimbra – Portugal
Marco Alves da Costa - Centro Hospitalar de Coimbra, Coimbra – Portugal
Maria João Soares Vidigal Teixeira Ferreira - Universidade de Coimbra, Coimbra – Portugal
Massimo Francesco Piepoli - Ospedale "Guglielmo da Saliceto", Piacenza – Italy
Nuno Bettencourt - Universidade do Porto, Porto – Portugal
Raffaele Giubbini - Università degli Studi di Brescia, Brescia – Italy
Ravi Kashyap - International Atomic Energy Agency, Vienna – Austria
Roberto José Palma dos Reis - Hospital Polido Valente, Lisboa – Portugal
Shekhar H. Deo - University of Missouri, Columbia – USA

BIENNIUM BOARD 2020/2021

SOCIEDADE BRASILEIRA DE CARDIOLOGIA/BRAZILIAN SOCIETY OF CARDIOLOGY

President
Marcelo Antônio Cartaxo Queiroga Lopes

Vice President
Celso Amodeo

Financial Director
Ricardo Mourilhe Rocha

Scientific Director
Fernando Bacal

Managing Director
Olga Ferreira de Souza

Service Quality Director
Sílvio Henrique Barberato

Communication Director
Harry Corrêa Filho

Information Technology Director
Leandro Ioschpe Zimerman

Governmental Relations Director
Nasser Sarkis Simão

State and Regional Relations Director
João David de Souza Neto

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

Director of Specialized Departments
Andréa Araujo Brandão

Research Director
David de Pádua Brasil

Coordinator of Science, Technology and Innovation
Ludhmila Abrahão Hajjar

Coordinator of Continued Medical Education
Brivaldo Markman Filho

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

Coordinator of Compliance and Transparency
Marcelo Matos Cascudo

Coordinator of Strategic Affairs
Hélio Roque Figueira

Editor-in-Chief of the International Journal of Cardiovascular Sciences
Claudio Tinoco Mesquita

Editor do IJCS
Claudio Tinoco Mesquita

Coordinator of the University of the Heart
Evandro Tinoco Mesquita

Coordinator of Standards and Guidelines
Paulo Ricardo Avancini Caramori

PRESIDENTS OF STATE AND REGIONAL BRAZILIAN SOCIETIES OF CARDIOLOGY

SBC/AL – Carlos Romerio Costa Ferro

SBC/AM – Kátia do Nascimento Couceiro

SBC/BA – Gilson Soares Feitosa Filho

SBC/CE – Gentil Barreira de Aguiar Filho

SBC/DF – Alexandra Oliveira de Mesquita

SBC/ES – Tatiane Mascarenhas Santiago Emerich

SBC/GO – Leonardo Sara da Silva

SBC/MA – Mauro José Mello Fonseca

SBC/MG – Henrique Patrus Mundim Pena

SBC/MS – Gabriel Doreto Rodrigues

SBC/MT – Marcos de Thadeu Tenuta Junior

SBC/NNE – Nivaldo Menezes Filgueiras Filho

SBC/PA – Dilma do Socorro Moraes de Souza

SBC/PB – Lenine Angelo Alves Silva

SBC/PE – Fernando Ribeiro de Moraes Neto

SBC/PI – Luiz Bezerra Neto

SBC/PR – Raul DAurea Mora Junior

SBC/RN – Maria Sanali Moura de Oliveira Paiva

SBC/SC – Amberson Vieira de Assis

SBC/SE – Eryca Vanessa Santos de Jesus

SOCERGS – Mario Wiehe

SOCERJ – Wolney de Andrade Martins

SOCERON – Daniel Ferreira Mugrabi

SOCESP – João Fernando Monteiro Ferreira

PRESIDENTS OF 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

Volume 34, Nº 4, July/August 2021
Indexing: Index Medicus Latino-Americano – LILACS and Scientific Electronic Library Online - SciELO

Commercial Department
Telephone Number: (11) 3411-5500
e-mail: comercialsp@cardiol.br

Editorial Production
SBC - Gerência Científica - Núcleo de Publicações

Desktop Publishing and Graphic Design
SBC - Tecnologia da Informação e Comunicação - Núcleo Interno de Design

Former SOCERJ Magazine (ISSN 0104-0758) up to December 2009; Revista Brasileira de Cardiologia (print ISSN 2177-6024 and online ISSN 2177-7772) from January 2010 up to December 2014.
International Journal of Cardiovascular Sciences (print ISSN 2359-4802 and online ISSN 2359-5647) from January 2015.

ÓRGÃO OFICIAL DA
SOCIEDADE BRASILEIRA DE CARDIOLOGIA - SBC
PUBLICAÇÃO BIMESTRAL / PUBLISHED BIMONTHLY
INTERNATIONAL JOURNAL OF CARDIOVASCULAR SCIENCES
(INT J CARDIOVASC SCI)

The International Journal of Cardiovascular Sciences (ISSN 2359-4802)
is published bimonthly by SBC:
Av. Marechal Câmara, 160 - 3º andar - Sala 330
20020-907 • Centro • Rio de Janeiro, RJ • Brazil
Tel.: (21) 3478-2700
e-mail: revistaijcs@cardiol.br
http://ijcscardiol.org/

INTERNATIONAL JOURNAL OF
Cardiovascular
SCIENCES

SUMARY

Int J Cardiovasc Sci. 2021; 34(4):336-337

PREFACE

Heart Disease is the Leading Cause of Death for Women – We must Change the Status Quo

Gláucia Maria Moraes de Oliveira[1] and Claudio Tinoco Mesquita [2,3,4]

Pós-graduação em Cardiologia da UFRJ, Universidade Federal do Rio de Janeiro (UFRJ),[1] Rio de Janeiro, RJ - Brazil
Pós-Graduação em Ciências Cardiovasculares, Ebserh/HUAP, Universidade Federal Fluminense,[2] Niterói, RJ - Brazil
Hospital Pró-Cardíaco,[3] Rio de janeiro, RJ – Brazil
Editor-in-Chief International Journal of Cardiovascular Sciences, Sociedade Brasileira de Cardiologia,[4] Rio de Janeiro, RJ - Brazil

According to the Continuous National Household Sample Survey, in 2019, the Brazilian population was composed of 48.2% men and 51.8% women. In the age group up to 24 years old, men and women accounted for 17.8% and 17.2% of the population, respectively, in 2019. From 25 years of age onwards, the proportion of women was higher than that of men in all age groups, 30.4% and 34.6%, respectively, for men and women. On the other hand, life expectancy for men in that same year was 73.1 years, and, for women, it was 80.1 years. Therefore, it is important to build data about Brazilian women in all stages of their course of life.[1]

The greatest burden of death and disability among women worldwide is attributable to non-communicable diseases, especially cardiovascular diseases (CVD). Moreover, nearly 80% of non-communicable diseases occur in low-income and middle-income countries, such as Brazil.[2] Marques-Santos and Oliveira highlighted the differences in CVD between female and male sex and emphasized the higher proportional mortality in Brazilian women.[3] According to Global Burden of Disease 2019, in Brazil, CVD accounted for 22.42% of deaths in women, compared to 20.83% in men, considering all ages.[4]

In the same line, Parapid & Bond highlight several aspects of the inequity unveiled by COVID-19 in women's lives, and they proposed actions to improve the careers of women in the frontline of the health-care sector. Finally, they conclude that "most importantly, as doctors, we know that, as long as there is a will, we tend to find a way, and, finally, if not us, then who?" That is our mission, to meet women where they are to provide better cardiovascular care.[5]

Several aspects of risk stratification in women have been shown in the original articles, especially those specific to the female sex, in a country like Brazil with different socioeconomic determinants. It is worth noting that cardiovascular risk in Brazilian women, mostly at young ages, has been changing in recent years, with increased obesity, diabetes, and arterial hypertension, in accordance with data from Global Burden of Disease 2019.[4] However, most of them are preventable by means of healthy lifestyles at the population and individual levels.

Women are underdiagnosed and undertreated compared to men with the worst prognosis in various diseases, such as ischemic heart disease, myocardial infarction, mitral valve diseases, and infective endocarditis, as we can see in the articles in this issue.[6-10]

Dr. Fausto Pinto, President of the World Heart Federation, highlighted the necessity of getting gender equity and listed several suggestions proposed by the ACC's Cardiovascular Disease in Women Committee to reduce existing gaps. And he emphasizes that "a lot has been done, but a lot more still needs to be done. It is up to all of us to ensure that will happen".[11]

Mailing Address: Gláucia Maria Moraes de Oliveira
Universidade Federal do Rio de Janeiro – R. Prof. Rodolpho P. Rocco, 255 – 8°. Andar – Sala 6, UFRJ. Postal Code 21941-913, Cidade Universitária, RJ – Brazil
E-mail: glauciam@cardiol.br

DOI: https://doi.org/10.36660/ijcs.20210185

Brazil is a continent-sized country with great heterogeneity and local diversity due to socioeconomic and cultural aspects of women's lives. Therefore, it is fundamental to promote initiatives to increase knowledge about the importance of cardiovascular health in all women's life courses. Furthermore, it is crucial to better understand local disparities in women's cardiovascular health in order to define public policy and health care, reduce gaps, and promote gender equity in Brazilian health care.[3]

We would like to thank Dr. Roxana Mehran, Professor of Medicine and Director of Interventional Cardiovascular Research and Clinical Trials at the Zena and Michael A. Wiener Cardiovascular Institute at Mount Sinai, for accepting the invitation to co-edit this issue. Dr. Mehran is an international leader in cardiology, and she is involved in multiple activities that contribute to the empowerment of women in cardiology and to coping with cardiovascular disease in women. In addition to our special thanks to Dr. Mehran, we extend our thanks to all editors, authors, reviewers, contributors, translators, statisticians, and members of the editorial board of the *International Journal of Cardiovascular Sciences* who have undertaken the enormous effort to bring us this special issue.

We invite you to read this special issue that intends to understand better all aspects of cardiovascular health care in women in order to give them healthy lives wherever they are. We greatly appreciate all the women who helped us build this special edition, especially Ms. Tailane Rodrigues, who put forth all her best efforts to bring us this outstanding issue of the *International Journal of Cardiovascular Sciences* completely devoted to Brazilian women.

Tailane Rodrigues
Editorial Assistant of the IJCS Journal
Postgraduate in Library Science
Fluminense Federal University (UFF),
Niterói, RJ - Brazil

References

1. Instituto Brasileiro de Geografia e Estatística. Pesquisa Nacional por Amostra de Domicílios Contínua - PNAD. Brasília: IBGE; 2019.
2. Oliveira GMM, Brant LCC, Polanczyk CA, Biolo A, Nascimento BR, Malta DC, et al. Cardiovascular Statistics - Brazil 2020. Arq Bras Cardiol. 2020;115(3):308-439. doi: 10.36660/abc.20200812.
3. Marques-Santos C, Oliveira GMM. Are Women the Fragile Sex? Or are They the Singular Sex? Int J Cardiovasc Sci. 2021; 34(4):344-346. doi: https://doi.org/10.36660/ijcs.20210171.
4. Global Burden of Disease Study 2019 (GBD 2019) Results. Global Health Data Exchange Website. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2019.
5. Parapid B, Bond RM. COVID-19: An Insult to Injury on Equity. Int J Cardiovasc Sci. 2021; 34(4):342-343. doi: https://doi.org/10.36660/ijcs.20210165.
6. Vogel B, Acevedo M, Appelman Y, Merz CNB, Chieffo A, Figtree GA, et al. The Lancet Women and Cardiovascular Disease Commission: Reducing the Global Burden by 2030. Lancet. 2021;397(10292):2385-438. doi: 10.1016/S0140-6736(21)00684-X.
7. Ferreira MCM, Oliveira MV, Paiva MSM, Lemke V, Mangione F, Oliveira GMM. Closing the Gender Gap in Ischemic Heart Diseases and Myocardial Infarction. Int J Cardiovasc Sci. 2021; 34(4):471-483 doi: https://doi.org/10.36660/ijcs.20210001.
8. Moreira JL, Barletta PHAAS, Baucia JA. Women Undergoing Mitral Valve Replacement: A Retrospective Analysis. Int J Cardiovasc Sci. 2021; 34(4):431-442. doi: https://doi.org/10.36660/ijcs.20200412.
9. Sousa C, Nogueira PJ, Pinto FJ. Gender Based Analysis of a Population Series of Patients Hospitalized with Infective Endocarditis in Portugal – How do Women and Men Compare? Int J Cardiovasc Sci. 2021; 34(4):347-355. doi: https://doi.org/10.36660/ijcs.20210032
10. Mehran R, Vogel B. Women and Cardiac Disease: A Special Issue. Int J Cardiovasc Sci. 2021; 34(4):338-339. doi: https://doi.org/10.36660/ijcs.20210173.
11. Pinto FJ. Gender Equity: Time to Act. Int J Cardiovasc Sci. 2021; 34(4):340-341.doi: https://doi.org/10.36660/ijcs.20210183.

Int J Cardiovasc Sci. 2021; 34(4):338-339

EDITORIAL

Women and Cardiac Disease: A Special Issue

Roxana Mehran and Birgit Vogel

Icahn School of Medicine at Mount Sinai, New York - USA

Cardiovascular disease is the leading cause of death in women worldwide. Despite improvements in awareness on heart disease in women through various campaigns and initiatives, cardiovascular risk in women still tends to be underestimated by health care professionals and women themselves. With respect to the latter, a study from the United States has even shown a decline in awareness regarding the fact that heart disease is the leading cause of death among women over recent years.[1] Especially young women are affected by low awareness about cardiovascular risk as confirmed by the data from the Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients (VIRGO) study, which also found that women are less likely than men to have a discussion about their cardiovascular risk and potential risk modification with their health care provider.[2] Health care providers' preparedness to assess women's cardiovascular risk appears to be suboptimal, and according to survey data the majority of primary care physicians and cardiologists do not comprehensively implement cardiovascular disease prevention guidelines in women.[3] Accurate and timely diagnosis of various cardiovascular diseases, especially ischemic heart disease, are less frequent in women compared with men. In addition, women with established cardiovascular disease have repeatedly been documented to be less likely to receive guideline-recommended therapies.[4,5] Sex-related differences in disease presentation and comorbidities may contribute to these disparities, and uncertainties persist with respect to diagnosis and treatment of certain disease states that disproportionally affect women (e.g. ischemia with non-obstructive coronary arteries [INOCA], myocardial infarction in the absence of obstructive coronary artery disease [MINOCA], spontaneous coronary artery dissection [SCAD], and takotsubo syndrome).

One of the major issues is the lack of robust study data on cardiovascular disease in women. Women remain underrepresented in the majority of cardiovascular clinical trials, and sex-specific study data reporting is often absent, which results in uncertainty about the safety and efficacy of many cardiovascular therapies.[6] In addition, it leads to knowledge gaps in the sex-specific pathophysiological mechanisms and the natural history of cardiovascular disease in women.

Cardiovascular risk factors may affect women differently than men, and there is growing evidence about risk factors specific to women, including premature menopause and pregnancy-related disorders.[7] Some studies also suggest that the association between cardiovascular risk and socioeconomic deprivation is more pronounced in women compared with men. Further investigation is urgently needed to evaluate the sex-specific impact of well-established risk factors, sex-specific conditions, and

Keywords

International Journal of Cardiovascular Sciences; Heart Diseases; Women.

Birgit Vogel, MD
Mount Sinai Morningside Hospital,
Icahn School of Medicine at Mount Sinai

Roxana Mehran, MD, FACC, FACP, FCCP, FESC, FAHA, FSCAI
Professor of Medicine and Director of Interventional Cardiovascular Research and Clinical Trials at the Zena and Michael A. Wiener Cardiovascular Institute at Mount Sinai School of Medicine

Mailing Address: Roxana Mehran
Icahn School of Medicine at Mount Sinai
One Gustave L. Levy Place, New York, NY – USA. Postal Code: 10029.
E-mail: Roxana.Mehran@mountsinai.org

DOI: https://doi.org/10.36660/ijcs.20210173

the direct and indirect effects of underrecognized factors, such psychosocial factors, on women's cardiovascular health. It should be one of the major research targets to better understand how to incorporate these factors in risk stratification tools and how to improve risk prediction, especially in young women.

Further research is also needed to investigate the role of sex hormones on cardiovascular risk in women. It is well documented that, in comparison with men, women generally present later in life with coronary artery disease and that cardiovascular risk increases significantly after menopause.[8] While data suggest that cardiovascular risk and the development of cardiovascular disease are impacted by endogenous and exogenous reproductive hormone differences, it is still not fully elucidated how sex-hormones affect the cardiovascular system in women. Despite the lower cardiovascular risk of young (premenopausal) women compared with their male counterparts, alarming trends have recently been documented, with a rise in myocardial infarction in young women[9] and an overall increase in cardiovascular disease mortality in women from certain countries.[10] It must be a priority to investigate the underlying reasons and find strategies to oppose these worrisome developments.

This special issue of the *International Journal of Cardiovascular Sciences* on cardiac disease in women features important research in women and heart disease; the original research articles include studies providing valuable insights on cardiovascular risk factors, risk classification, and risk profiles of women from certain age groups and geographical areas. Furthermore, this issue comprises data on women traversing menopause, which marks a critical time of cardiovascular risk acceleration in a woman's life, and it addresses cardiovascular risk in the growing population of breast cancer survivors. A comprehensive literature review on sex and gender differences in ischemic heart disease as well as interesting case reports are among the other high-yield articles in this issue. Providing a platform for research on cardiovascular disease in women in this way is a crucial step to inform the medical and scientific communities, to raise awareness, and to motivate further studies on this important topic. A robust and comprehensive evidence base on cardiovascular disease in women is the cornerstone of providing optimal care to women and reducing the global burden of cardiovascular disease. This special issue on cardiac disease in women is an important effort in addressing the gender gap and developing sex-specific strategies for improved prevention, diagnosis, and treatment of cardiovascular disease worldwide.

References

1. Cushman M, Shay CM, Howard VJ, Jiménez MC, Lewey J, McSweeney JC, et al. Ten-Year Differences in Women's Awareness Related to Coronary Heart Disease: Results of the 2019 American Heart Association National Survey: A Special Report From the American Heart Association. Circulation. 2021;143(7):239-48. doi: 10.1161/CIR.0000000000000907.

2. Leifheit-Limson EC, D'Onofrio G, Daneshvar M, Geda M, Bueno H, Spertus JA, et al. Sex Differences in Cardiac Risk Factors, Perceived Risk, and Health Care Provider Discussion of Risk and Risk Modification Among Young Patients with Acute Myocardial Infarction: The VIRGO Study. J Am Coll Cardiol. 2015;66(18):1949-57. doi: 10.1016/j.jacc.2015.08.859.

3. Merz CNB, Andersen H, Sprague E, Burns A, Keida M, Walsh MN, et al. Knowledge, Attitudes, and Beliefs Regarding Cardiovascular Disease in Women: The Women's Heart Alliance. J Am Coll Cardiol. 2017;70(2):123-32. doi: 10.1016/j.jacc.2017.05.024.

4. Redfors B, Angerås O, Råmunddal T, Petursson P, Haraldsson I, Dworeck C, et al. Trends in Gender Differences in Cardiac Care and Outcome After Acute Myocardial Infarction in Western Sweden: A Report from the Swedish Web System for Enhancement of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). J Am Heart Assoc. 2015;4(7):e001995. doi: 10.1161/JAHA.115.001995.

5. Udell JA, Fonarow GC, Maddox TM, Cannon CP, Peacock WF, Laskey WK, et al. Sustained Sex-Based Treatment Differences in Acute Coronary Syndrome Care: Insights from the American Heart Association get with The Guidelines Coronary Artery Disease Registry. Clin Cardiol. 2018;41(6):758-68. doi: 10.1002/clc.22938.

6. Jin X, Chandramouli C, Allocco B, Gong E, Lam CSP, Yan LL. Women's Participation in Cardiovascular Clinical Trials From 2010 to 2017. Circulation. 2020;141(7):540-8. doi: 10.1161/CIRCULATIONAHA.119.043594.

7. Agarwala A, Michos ED, Samad Z, Ballantyne CM, Virani SS. The Use of Sex-Specific Factors in the Assessment of Women's Cardiovascular Risk. Circulation. 2020;141(7):592-9. doi: 10.1161/CIRCULATIONAHA.119.043429.

8. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of Potentially Modifiable Risk Factors Associated with Myocardial Infarction in 52 Countries (the INTERHEART study): Case-Control Study. Lancet. 2004;364(9438):937-52. doi: 10.1016/S0140-6736(04)17018-9.

9. Arora S, Stouffer GA, Kucharska-Newton AM, Qamar A, Vaduganathan M, Pandey A, et al. Twenty Year Trends and Sex Differences in Young Adults Hospitalized with Acute Myocardial Infarction. Circulation. 2019;139(8):1047-56. doi: 10.1161/CIRCULATIONAHA.118.037137.

10. Lopez AD, Adair T. Is the Long-Term Decline in Cardiovascular-Disease Mortality in High-Income Countries Over? Evidence from National Vital Statistics. Int J Epidemiol. 2019;48(6):1815-23. doi: 10.1093/ije/dyz143.

Int J Cardiovasc Sci. 2021; 34(4):340-341

EDITORIAL

Gender Equity: Time to Act

Fausto J. Pinto[1,2]

President, World Heart Federation,[1] Geneva - Switzerland
Universidade de Lisboa,[2] Lisboa - Portugal

This issue of the International Journal of Cardiovascular Sciences comes at a time when the medical and scientific community are finally addressing an important issue that has been somehow neglected over the years. That is gender equity when dealing with health and scientific issues. This relates not only with the medical differences between genders in many clinical conditions, but also how gender equity is still an enormous issue when we are dealing with health care forces, payments, access to leading positions and many other aspects,[1,2] including citations in high-impact journals.[3]

Scientific societies have developed several initiatives in order to address some of these issues. At the European Society of Cardiology (ESC) several initiatives were organized over the years, including creation of a working group on "Women in Cardiology", support of the "Leadership for women" Program organized by Oxford University, where several ESC female leaders were supported. Some Associations created specific committees, such as the Interventional Cardiology Association (EAPCI Women Committee) that was created in December 2013.[4] On International Women's Day (8th March 2011), the European Society of Cardiology (ESC) launched a call for action to reduce the gender disparities that are currently resulting in women receiving second rate cardiovascular (CV) care.[5] Studies published online on that day in the European Heart Journal (EHJ),[6,7] the official journal of the ESC, showed a persistent under-utilisation of guideline recommended treatments for heart disease in women compared to men. Unfortunately not much has changed over the last years.[8]

In the USA, American Heart Association (AHA) and American College of Cardiology (ACC) have also developed very relevant initiatives and projects related with gender inequities and some of them have really helped to increase the awareness on the issue, such as the program "Go Red for Women",[9] as well as helping shaping formal decisions to help promoting gender equity.

In a remarkable study (systematic review) from ACC's Cardiovascular Disease in Women Committee, they concluded female physicians have better patient outcomes compared with their male peers, while female patients are less likely to receive guideline-recommended care when treated by a male physician.[10] While care disparities can be attributed to multiple factors, they may relate, in part, to the differences in how cardiovascular disease presents in women vs. men, the underrepresentation of female subjects in clinical trials and the lack of women's health training in U.S. medical education.[11] To combat these findings, the study authors proposed three major recommendations, that I underline here:

1. Increasing Gender Diversity in the Physician Workforce

- Create interventions designed to address existing implicit and explicit biases which have limited opportunities for women in cardiovascular medicine.

Keywords

Gender Equity; Gender Diversity ; Sex.

Fausto J. Pinto - MD, PhD, FESC, FACC, FSCAI, FASE
President, World Heart Federation
Universidade de Lisboa - Portugal

Mailing Address: Fausto J. Pinto
Faculdade de Medicina da Universidade de Lisboa
Av Prof. Egas Moniz. Postal Code: 1649-028 Lisboa - Portugal
E-mail: faustopinto@medicina.ulisboa.pt
twitter: @fjpinto1960

DOI: https://doi.org/10.36660/ijcs.20210183

- Change the culture of cardiology to be more female- and family-friendly.
- Increase representation of women in leadership positions in cardiovascular medicine.

2. Improving Gender- and Sex-Specific Medical Training

- Focus curricula on the presentation, diagnosis and treatment of women and men, and highlight specific differences.
- Include comprehensive behavioral health curriculum to address stress, depression and anxiety faced by women, as well as men, with cardiovascular disease.
- Teach patient-centered communication styles.
- Introduce implicit bias training.

3. Increase Research on the Role of Gender in Patient-Physician Relationships

- Focus on nonrandomized experimental designs that incorporate economic approaches with medical research.

The World Heart Federation (WHF) as a global organization in official relation with WHO is involved and encouraging several programmes where gender equity is a major concern. A good example is a join project with our members the Colombian Society of Cardiology and the Colombian Heart Foundation called "Act with a woman's heart".[12] The aim is to empower women health professionals and female leaders in black communities in Monteria, Cartajena and Apartado – underserved communities with high rates of NCDs among women – to prevent and manage heart disease. The main activities will include online training, health screenings and follow-up with a focus on hypertension, support groups for adherence to medication & lifestyle recommendations, and awareness campaigns.The project started in October 2020. By the end of 2021, we expect to reach 800-1000 women health professionals nationwide and 450 women health leaders in the three communities.

It is, therefore, fundamental to continue to implement measures that help to reduce and, hopefully, end with all the gaps related with gender inequities. This is a long standing commitment that the whole scientific community should subscribe and particularly their leadership should encourage, nurture and implement. A lot has been done but a lot more still needs to be done. It is up to all of us to ensure that will happen. This initiative of the International Journal of Cardiovascular Sciences is certainly on that way and deserves our recognition and gratitude to the Brazilian Cardiovascular Community.

References

1. Westerman S, Wenger NK. Women and Heart Disease, the Underrecognized Burden: Sex Differences, Biases, and Unmet Clinical and Research Challenges. Clin Sci. 2016;130(8):551-63. doi: 10.1042/CS20150586.
2. Kuehn BM. State of the Heart for Women. Circulation. 2019;139(8):1121-3. doi: 10.1161/CIRCULATIONAHA.118.039372.
3. Chatterjee P, Werner RM. Gender Disparity in Citations in High-Impact Journal Articles. JAMA Netw Open. 2021;4(7):e2114509. doi: 10.1001/jamanetworkopen.2021.14509.
4. EAPCI Women Committee [Internet] Brussels: Europe Society of Cardiology; c2021 [cited 2021 Jul 05]. Available from: https://www.escardio.org/Sub-specialty-communities/European-Association-of-Percutaneous-Cardiovascular-Interventions-(EAPCI)/Membership-and-Communities/The-EAPCI-Women-Initiative.
5. EAPCI Women Committee [Internet] Brussels: Europe Society of Cardiology; c2021 [cited 2021 Jul 05]. Available from: https://www.escardio.org/The-ESC/Press-Office/Press-releases/International-Women-s-Day-provides-a-red-alert-for-women-s-hearts.
6. Johnston N, Schenck-Gustafsson K, Lagerqvist B. Are We Using Cardiovascular Medications and Coronary Angiography Appropriately in Men and Women with Chest Pain? Eur Heart J. 2011;32(11):1331-6. doi: 10.1093/eurheartj/ehr009.
7. Bugiardini R, Yan AT, Yan RT, Fitchett D, Langer A, Manfrini O, et al. Factors Influencing Underutilization of Evidence-Based Therapies in Women. Eur Heart J. 2011;32(11):1337-44. doi: 10.1093/eurheartj/ehr027.
8. Sciomer S, Moscucci F, Dessalvi CC, Deidda M, Mercuro G. Gender Differences in Cardiology: Is it Time for New Guidelines? J Cardiovasc Med. 2018;19(12):685-8. doi: 10.2459/JCM.0000000000000719.
9. Go Red for Women [Internet] Dallas: American Heart Association; c2021 [cited 2021 Jul 5]. Available from: https://www.goredforwomen.org/en.
10. Lau ES, Hayes SN, Volgman AS, Lindley K, Pepine CJ, Wood MJ, et al. Does Patient-Physician Gender Concordance Influence Patient Perceptions or Outcomes? J Am Coll Cardiol. 2021;77(8):1135-8. doi: 10.1016/j.jacc.2020.12.031.
11. Do Female CV Disease Patients with Female Physicians Fare Better? [Internet] Washington: American College of Cardiology; c2021 [cited 2021 Jul 5]. Available from: https://www.acc.org/latest-in-cardiology/articles/2021/02/22/19/50/do-female-cv-disease-patients-with-female-physicians-fare-better.
12. Taking Action for Women's Cardiovascular Health in Colombia [Internet] Geneva: World Heart Federation; c2021 [cited 2021 Jul 5]. Available from: https://world-heart-federation.org/news/taking-action-for-womens-cardiovascular-health-in-colombia/.

Int J Cardiovasc Sci. 2021; 34(4):342-343

EDITORIAL

COVID-19: An Insult to Injury on Equity

Biljana Parapid[1] and Rachel M. Bond[2,3]

Belgrade University School of Medicine, Division of Cardiology University Clinical Center of Serbia,[1] Belgrade - Serbia
Dignity Health System, Division of Cardiology,[2] Chandler, AZ - USA
Creighton University School of Medicine, Division of Internal Medicine,[3] Omaha, NE - USA

SARS-CoV-2, which causes COVID-19, created a pandemic that not only overwhelmed the world in December 2019, but also challenged humanity in every way.

While a significant portion of the global population remained in a standstill, waiting for an end and adapting to limits of all sorts, including working from home, a new workforce category emerged: the "frontline" workers. Doctors, nurses, and all allied professions employed by the healthcare system were joined by a long line of diverse service providers. The latter faced different forms of discrimination from their surroundings, fearing the risk of infection based on high rates of medical misinformation; for the former group, Pandora's box of bias was yet to be opened, in particular for women.

According to initial reports, women were less likely to develop severe or life-threatening forms of SARS-CoV-2 infection. With higher mortality rates seen in men, an assumption that frontline work was safer for women than men quickly emerged. As a result, although scarce, reports confirmed higher infection rates in women frontline healthcare workers, as was seen in Spain.[1]

Keywords

COVID19; Equity; SARS-CoV-2; Diversity; Inclusion.

Mailing Address: Biljana Parapid, MD, PhD, FESC
Assistant Professor, Department of Internal Medicine - Cardiology
School of Medicine University of Belgrade
Division of Cardiology, University Clinical Center of Serbia
Dr. Subotića, 13. Postal Code: 11000 Beograd - Serbia
Email: biljana_parapid@yahoo.com

DOI: https://doi.org/10.36660/ijcs.20210165

Globally, women occupy 70% of frontline positions in the healthcare sector. Despite this, they are paid 11% less than men.[2] This was reconfirmed during the pandemic, where women physicians and nurses in the United States were paid 12% and 8% less than men in the same positions.[3] Yet, only 25% of healthcare leadership and decision-making positions have been held by women during the pandemic.[4]

The first warnings came from UN Women in early Spring 2020.[5] With the significantly higher percentage of women frontline workers, an ongoing crisis will only deepen gaps on the road to achieving equity. This was best highlighted where, simultaneously, various international medical entities[6] yielded additional attention to the world of academic medicine where tenure clocks were not stopped or even paused, further aggravating promotion pathways for women who had less time to publish. Additionally, while men were not participating in frontline work, they were afforded the opportunity to be lead authors of publications on frontline work and/or ongoing pandemic research.[7]

The existing unpaid workload at home was globally aggravated by the increased need for homeschooling, and, culturally, while dual physician households experienced additional challenges during pandemic work, the toll on women's health were universally greater: from mental health issues to delayed family planning due to menstrual cycle disturbances, [8-13] even in the absence of contracting the disease itself or while recovering from it.

Finally, as the pandemic has greatly changed our existence, lamenting and reporting well-known data should give way to implementation of actionable solutions.

"*Primum non nocere*." Medical academic institutions should start by practicing what they preach, beginning

Biljana Parapid, MD, PhD, FESC
Assistant Professor, Department of Internal Medicine - Cardiology
School of Medicine University of Belgrade
Division of Cardiology, University Clinical Center of Serbia

Rachel M.Bond, FACC
System Director, Women's Heart Health
Dignity Health, Chandler, AZ - USA
Creighton University School of Medicine, Division of Internal Medicine, Omaha, NE - USA

with their employees, the same way they do for their patients, regardless of gender, color, or creed. As women's healthcare policies vary globally,[14] it is up to the leading medical and scientific authorities of each respective country – *regardless of local practice and of whether or not there is a Diversity-Equity-Inclusion officer/vice-dean* – to protect their largest frontline workforce. Existing women's heart health programs, centers, and clinics should open their doors on a weekly basis to in-house staff, who most likely do not have time to schedule an appointment themselves. The potential budgeting issue could be overcome by the academic institution's dedicated burnout prevention program, and, in the event that there is no help from existing employee support models,[15] there is no better moment in the history of modern medicine than now to start one. For what it is worth, as always and everywhere, a group of volunteers who are willing to see patients *pro bono* will quickly appear; so why not start with one's own colleagues?

As the face of education continues to change, with pressing needs to offer various forms of teaching to our students, committees that handle academic promotions have had plenty of time to consider involvement in frontline work – *and more importantly lack thereof* – as well as existing engagement in virtual teaching.

One solution is the creation of a new category of achievement points for candidates, especially for those who have actively participated in all pandemic-related activities from the beginning, as well as for colleagues who suffered from workplace-acquired COVID-19.

Even in the setting where groups of junior or mid-career academics are promoted together, it may be best to delay the promotion of a pandemic bystander for the benefit of an active participant.

This logic can only promote a healthier work environment in the long run, where no one will feel that they are being "left behind" because they are "unworthy".

Most importantly, as doctors, we know that, as long as there is a will, we tend to find a way, and, finally, if not us, then who?

References

1. In Spain, infection cases of COVID-19 are twice as high among female health workers. Source: UN Women calculation based on data from Spain's Ministry of Health: Analisis epidemiologico Covid-19, as of 30 March 2020. In: @unwomen, editor.
2. Boniol MM, M.; Xu, L.; Wuliji, T.; Diallo, K.; Campbell, J. Gender Equity in the Health Workforce: Analysis of 104 countries. Geneva: World Health Organization; 2019.
3. Wilson V. Exposed and Underpaid: Women Still Make less than Men, Including in Sectors Especially Affected by the Coronavirus [Internet]. Economic Policy Institute; 2020 [cited 2021 Jun 23]. Available from: https://www.epi.org/blog/exposed-and-underpaid-women-still-make-less-than-men-including-in-sectors-especially-affected-by-the-coronavirus/.
4. Freizer S. COVID-19 and Women's Leadership: From an Effective Response to Building Back Better. New York: United Nations Entity for Gender Equality and the Empowerment of Women (UN Women); 2020.
5. Azcona GB A, Davies S, Harman S, Smith J, Wenham C. COVID-Spotlight on gender, COVID-19 and the SDGs: Will the Pandemic Derail Hard-Won Progress on Gender Equality? New York: United Nations Entity for Gender Equality and the Empowerment of Women (UN Women); 2020.
6. Parapid B, Alasnag M, Hayes SN, Samargandy S, Banerjee S, Alasnag M, et al. COVID-19 Impact on Women on Both Sides of the Frontline – the American College of Cardiology Women in Cardiology Section's International Working Group Perspective. Srpski Arhiv za Celokupno Lekarstvo. 2020;148(9-10):637-42. doi: 10.2298/SARH200828095P.
7. DeFilippis EM, Sinnenberg L, Mahmud N, Wood MJ, Hayes SN, Michos ED, et al. Gender Differences in Publication Authorship During COVID-19: A Bibliometric Analysis of High-Impact Cardiology Journals. J Am Heart Assoc. 2021;10(5):e019005. doi: 10.1161/JAHA.120.019005.
8. Alhurishi SA, Almutairi KM, Vinluan JM, Aboshaiqah AE, Marie MA. Mental Health Outcomes of Healthcare Providers During COVID-19 Pandemic in Saudi Arabia: A Cross-Sectional Study. Front Public Health. 2021;9:625523. doi: 10.3389/fpubh.2021.625523.
9. Adibi A, Golitaleb M, Farrahi-Ashtiani I, Pirani D, Yousefi K, Jamshidbeigi Y, et al. The Prevalence of Generalized Anxiety Disorder Among Health Care Workers During the COVID-19 Pandemic: A Systematic Review and Meta-Analysis. Front Psychiatry. 2021;12:658846. doi: 10.3389/fpsyt.2021.658846.
10. Takmaz T, Gundogmus I, Okten SB, Gunduz A. The Impact of COVID-19-Related Mental Health Issues on Menstrual Cycle Characteristics of Female Healthcare Providers. J Obstet Gynaecol Res. 2021; Epub ahead of print. doi: 10.1111/jog.14900.
11. Shahbaz S, Ashraf MZ, Zakar R, Fischer F. Psychosocial, Emotional and Professional Challenges Faced By Female Healthcare Professionals during the COVID-19 Outbreak in Lahore, Pakistan: A Qualitative Study. BMC Womens Health. 2021;21(1):197. doi: 10.1186/s12905-021-01344-y.
12. Khan N, Palepu A, Dodek P, Salmon A, Leitch H, Ruzycki S, et al. Cross-Sectional Survey on Physician Burnout During the COVID-19 Pandemic in Vancouver, Canada: The Role of Gender, Ethnicity and Sexual Orientation. BMJ Open. 2021;11(5):e050380. doi: 10.1136/bmjopen-2021-050380.
13. Marvaldi M, Mallet J, Dubertret C, Moro MR, Guessoum SB. Anxiety, Depression, Trauma-Related, and Sleep Disorders among Healthcare Workers During the COVID-19 Pandemic: A Systematic Review and Meta-Analysis. Neurosci Biobehav Rev. 2021;126:252-64. doi: 10.1016/j.neubiorev.2021.03.024.
14. Kouvari M, Souliotis K, Yannakoulia M, Panagiotakos DB. Cardiovascular Diseases in Women: Policies and Practices Around the Globe to Achieve Gender Equity in Cardiac Health. Risk Manag Healthc Policy. 2020;13:2079-94. doi: 10.2147/RMHP.S264672.
15. Lamb D, Simms A, Greenberg N, Withnall RDJ. Caring for the Carers: a COVID-19 Psychological Support Programme. BMJ Mil Health. 2021:bmjmilitary-2021-001854. doi: 10.1136/bmjmilitary-2021-001854.

Int J Cardiovasc Sci. 2021; 34(4):344-346

EDITORIAL

Are Women the Fragile Sex? Or are They the Singular Sex?

Celi Marques-Santos[1] and Gláucia Maria Moraes de Oliveira[2]

Universidade Tiradentes,[1] Aracaju, SE – Brazil
Universidade Federal do Rio de Janeiro,[2] Rio de Janeiro, RJ – Brazil

Women need specific intervention and information about their particularities, especially regarding CV risk factors, as well as the biological, pathophysiological, and social differences between the sexes. The majority of large clinical trials that address current cardiovascular diseases (CVD) were not conducted with enough women to generate robust evidence.[1] CVD in women remains poorly studied, poorly recognized, underdiagnosed, and undertreated, generating worse outcomes. It is necessary to change this reality so that women are approached according to their singularities in order to reduce the burden of CVD by 2030.[2]

Among the CV risk factors in Brazilian women, arterial hypertension, dietary risks, obesity, increased serum cholesterol, and fasting glucose stand out.[3] Sex-related CV risk factors, which affect CVD throughout life, play a crucial role in women. [4] Menopause, especially in women 40 years, promotes changes in body composition, with an increase in fat mass and a greater probability of metabolic syndrome.[5,6] Hypertensive diseases of pregnancy, such as pre-eclampsia, gestational diabetes, and premature birth, increase CVD in adulthood.[7] The use of contraceptive hormones associated with arterial hypertension increases the risk of myocardial infarction (MI) by 12 times.[8] Polycystic ovary syndrome and autoimmune diseases contribute to increased cardiovascular risk.[9]

Other CV risk factors are more prevalent in women than men. Depression and anxiety promote a higher occurrence of obstructive and non-obstructive coronary heart disease and are associated with worse CV outcomes.[10] Domestic violence increases physical and mental stress, CV risk factors, smoking, obesity, depression, and anxiety, amplifying the risk of CVD.[11] Low educational level and low socioeconomic status elevate cardiovascular risk preponderantly in women.[12,13] All these CV risk factors need to be considered in the stratification of women, and they are not included in the available risk scores.[14] There is an urgent need to increase CVD risk stratification among primary care physicians and cardiologists. A study carried out in 2014 showed that less than 40% of these professionals felt well prepared to address CVD in women, and less than a quarter had comprehensively implemented prevention guidelines for CVD in women.[15]

The presentation of CVD in women has particularities that need to be recognized and treated. Ischemia resulting from non-obstructive coronary artery disease (INOCA) is prevalent in women, as a result of endothelial dysfunction, and it has adverse outcomes because it is poorly recognized and undertreated.[16] The same happens with MI in the absence of obstructive coronary artery disease (MINOCA), with spontaneous dissection of the coronary arteries, with MI without ST-segment elevation, which adds to the difficulties of implementing secondary prevention measures.[17] Peripheral vascular disease is underdiagnosed and undertreated, especially in low- and middle-income countries. Stroke resulting from hypertensive diseases and atrial fibrillation at advanced ages is prevalent in women, with worse outcomes. Cognitive deficits and dementia stand out, with increased burden of CVD.[18]

Regarding myocardial disease, there is a higher prevalence of heart failure with preserved ejection fraction,

Celi Marques Santos, MD
President of the Department of Women's Cardiology - SBC

Keywords

Cardiovascular Diseases; Women; Women's Health.

Mailing Address: Gláucia Maria Moraes de Oliveira
Universidade Federal do Rio de Janeiro – R. Prof. Rodolpho P. Rocco, 255 – 8°. Andar – Sala 6, UFRJ. Postal Code: 21941-913, Cidade Universitária, RJ – Brazil
E-mail: glauciam@cardiol.br

DOI: https://doi.org/10.36660/ijcs.20210171

Takotsubo syndrome, and peripartum cardiomyopathy, all with few therapeutic options based on multicenter and randomized clinical trials.[2,9] The rheumatic diseases and valvular sequelae are highlighted by the higher prevalence in women. With the aging of the population, they are added to aortic stenosis, which presents singularities such as a smaller valve ring and greater calcium deposition, requiring new strategies for the use of transcatheter aortic valve implantation.[19] Furthermore, cardiorespiratory arrest in women occurs predominantly at home, with a low rate of effective resuscitation due to defibrillation of ventricular arrhythmias.[20]

Despite the recognition of the importance of sex and gender in CVD research, important knowledge gaps persist. A review of cardiovascular trials included in the Cochrane Reviews reveals that only 27% of the total participants in 258 trials were women.[21] Adequate inclusion of women in research, coupled with adequate design and full reporting on adverse effects, requires joint effort on the part of funders, researchers, reviewers, and editors. In 2016, a panel of 13 experts from 9 countries developed the Sex and Gender Equity in Research (SAGER) guidelines intended to guide gender/sex information in study design and data analysis.[22]

In this context of so many gaps, women are far from receiving an ideal cardiology approach. Therefore, more inclusion is needed in clinical trials, as are validated risk scores that include specific CV risk factors.[23] Moreover, all segments of society must be involved, in order to seek customized solutions for each country.

According to Global Burden of Disease data, in Brazil, in 2019, ischemic heart disease and stroke accounted for 12.03% (95% uncertainty interval [UI] 10.66% – 12.88%) and 10.39% (95% UI 9.25% – 11.15%) of deaths from CVD in women, compared to 12.22% (95% UI 11.5% – 12.77%) and 8.41% (95% UI 7.84% – 8.83%) in men, respectively (Figure 1). To reduce the burden of CVD, the Brazilian Unified Health System is available, with access to three levels of care: primary, secondary, and tertiary. Primary Health Care and the Family Health Strategy are distributed throughout 5,570 municipalities, covering 76.08% of the Brazilian population, as of December 2020 (https://egestorab.saude.gov.br/ pages/ access public/reports/relHistoricoCoberturaAB.xhtml). Actions aimed at Primary Health Care would bring a good opportunity to improve awareness of CVD risks in women, encouraging primary prevention of their CV risk factors.

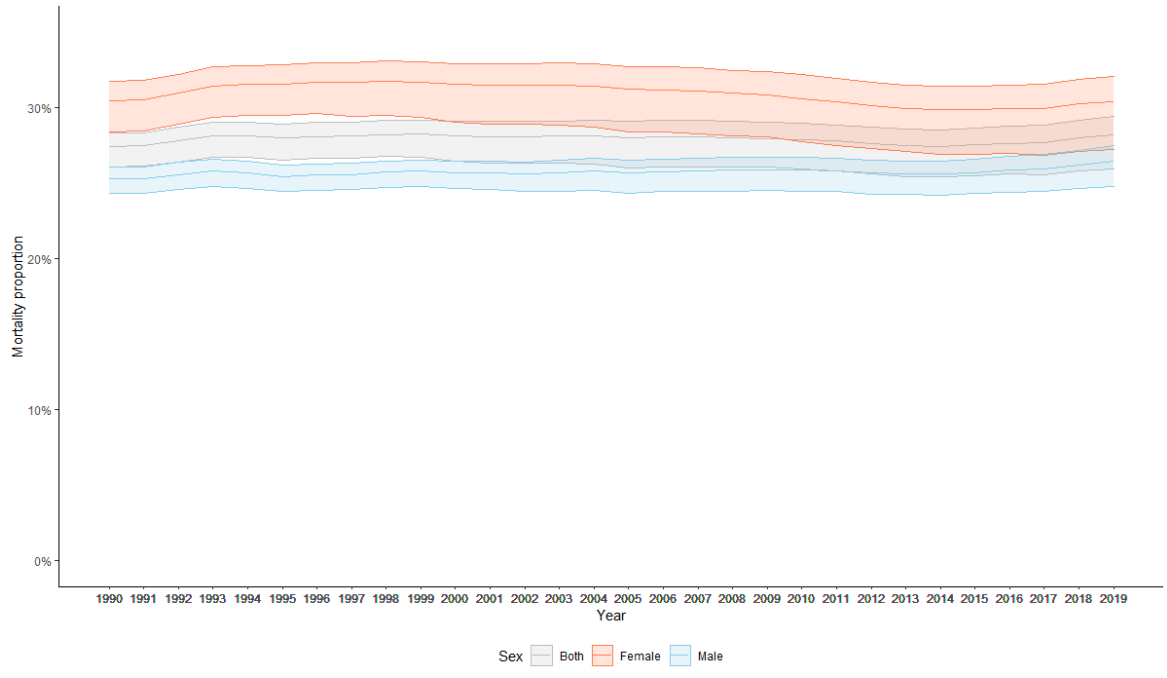


Figure 1 – Proportional mortality for cardiovascular diseases, by sex, Brazil, 1990 to 2019, Global Burden of Disease Study 2019. (https://vizhub.healthdata.org/gbd-compare/)

The creation of a Continuing Assisted Education Program for Women, focusing on CVD, developed by specialist societies, such as cardiology, gynecology, and obstetrics, aimed at Primary Health Care and the Family Health Strategy, could help implement diagnosis and treatment protocols of CV risk factors. Additionally, the construction of a nationwide database with indicators generated by the program would guide future interventions.

Another action to be taken would be dissemination and adherence to the SAGER guidelines on the part of national journals, with the publication of works that promote greater inclusion of women in order to generate therapeutic strategies with robust evidence. It is also necessary for funding agencies to develop programs that include women researchers who aim to conduct studies that can reduce CVD burden and mortality by the next decade, preventing undesirable outcomes, illness, and premature death in women.

The global agenda for women's health needs to be broadened and redefined, and a sex-disaggregated approach to health research and policy is required.[4] Therefore, women are not fragile sex; women are singular and must be seen and treated like that.

References

1. Scott PE, Unger EF, Jenkins MR, Southworth MR, McDowell TY, Geller RJ, et al. Participation of Women in Clinical Trials Supporting FDA Approval of Cardiovascular Drugs. J Am Coll Cardiol. 2018;71(18):1960-69. doi: 10.1016/j.jacc.2018.02.070.
2. Vogel B, Acevedo M, Appelman Y, Bairey Merz CN, Chieffo A, Figtree GA, et al. The Lancet Women and Cardiovascular Disease Commission: Reducing the Global Burden by 2030. Lancet. 2021;397(10292):2385-438. doi: 10.1016/S0140-6736(21)00684-X.
3. Oliveira GMM, Brant LCC, Polanczyk CA, Biolo A, Nascimento BR, Malta DC, et al. Cardiovascular Statistics - Brazil 2020. Arq Bras Cardiol. 2020;115(3):308-439. doi: 10.36660/abc.20200812.
4. Peters SA, Woodward M. Women's Reproductive Factors and Incident Cardiovascular Disease in the UK Biobank. Heart. 2018;104(13):1069-75. doi: 10.1136/heartjnl-2017-312289.
5. Greendale GA, Sternfeld B, Huang M, Han W, Karvonen-Gutierrez C, Ruppert K, et al. Changes in Body Composition and Weight During the Menopause Transition. JCI Insight. 2019;4(5):e124865. doi: 10.1172/jci.insight.124865.
6. Honigberg MC, Zekavat SM, Aragam K, Finneran P, Klarin D, Bhatt DL, et al. Association of Premature Natural and Surgical Menopause With Incident Cardiovascular Disease. JAMA. 2019;322(24):2411-21. doi: 10.1001/jama.2019.19191.
7. Timpka S, Fraser A, Schyman T, Stuart JJ, Åsvold BO, Mogren I, et al. The Value of Pregnancy Complication History for 10-year Cardiovascular Disease Risk Prediction in Middle-Aged Women. Eur J Epidemiol. 2018;33(10):1003-10. doi: 10.1007/s10654-018-0429-1.
8. Curtis KM, Mohllajee AP, Martins SL, Peterson HB. Combined oral Contraceptive Use Among Women With Hypertension: A Systematic Review. Contraception. 2006;73(2):179-88. doi: 10.1016/j.contraception.2005.08.005.
9. Young L, Cho L. Unique Cardiovascular Risk Factors in Women. Heart. 2019;105(21):1656-60. doi: 10.1136/heartjnl-2018-314268.
10. O'Neil A, Fisher AJ, Kibbey KJ, Jacka FN, Kotowicz MA, Williams LJ, et al. Depression is a risk factor for incident coronary heart disease in women: An 18-year longitudinal study. J Affect Disord. 2016;196:117-24. doi: 10.1016/j.jad.2016.02.029.
11. Wright EN, Hanlon A, Lozano A, Teitelman AM. The Association Between Intimate Partner Violence and 30-Year Cardiovascular Disease Risk Among Young Adult Women. J Interpers Violence. 2021;36(11-12):NP6643-NP6660. doi: 10.1177/0886260518816324.
12. Greenberg KL, Leiter E, Donchin M, Agbaria N, Karjawally M, Zwas DR. Cardiovascular Health Literacy and Patient-Physician Communication Intervention in Women from Disadvantaged Communities. Eur J Prev Cardiol. 2019;26(16):1762-70. doi: 10.1177/2047487319853900.
13. Backholer K, Peters SAE, Bots SH, Peeters A, Huxley RR, Woodward M. Sex Differences in the Relationship Between Socioeconomic Status and Cardiovascular Disease: A Systematic Review and Meta-Analysis. J Epidemiol Community Health. 2017;71(6):550-7. doi: 10.1136/jech-2016-207890.
14. Agarwala A, Michos ED, Samad Z, Ballantyne CM, Virani SS. The Use of Sex-Specific Factors in the Assessment of Women's Cardiovascular Risk. Circulation. 2020;141(7):592-9. doi: 10.1161/CIRCULATIONAHA.119.043429.
15. Merz CNB, Andersen H, Sprague E, Burns A, Keida M, Walsh MN, et al. Knowledge, Attitudes, and Beliefs Regarding Cardiovascular Disease in Women: The Women's Heart Alliance. J Am Coll Cardiol. 2017;70(2):123-32. doi: 10.1016/j.jacc.2017.05.024.
16. Reynolds HR, Shaw LJ, Min JK, Spertus JA, Chaitman BR, Berman DS, et al. Association of Sex with Severity of Coronary Artery Disease, Ischemia, and Symptom Burden in Patients with Moderate or Severe Ischemia: Secondary Analysis of the ISCHEMIA Randomized Clinical Trial. JAMA Cardiol. 2020;5(7):773-86. doi: 10.1001/jamacardio.2020.0822.
17. Haider A, Bengs S, Luu J, Osto E, Siller-Matula JM, Muka T, et al. Sex and Gender in Cardiovascular Medicine: Presentation and Outcomes of Acute Coronary Syndrome. Eur Heart J. 2020;41(13):1328-36. doi: 10.1093/eurheartj/ehz898.
18. Wenger NK, Arnold A, Merz CNB, Cooper-DeHoff RM, Ferdinand KC, Fleg JL, et al. Hypertension Across a Woman's Life Cycle. J Am Coll Cardiol. 2018;71(16):1797-813. doi: 10.1016/j.jacc.2018.02.033.
19. Mehta PK, Bess C, Elias-Smale S, Vaccarino V, Quyyumi A, Pepine CJ, et al. Gender in Cardiovascular Medicine: Chest Pain and Coronary Artery Disease. Eur Heart J. 2019;40(47):3819-26. doi: 10.1093/eurheartj/ehz784.
20. Blom MT, Oving I, Berdowski J, van Valkengoed IGM, Bardai A, Tan HL. Women Have Lower Chances than Men to be Resuscitated and Survive Out-Of-Hospital Cardiac Arrest. Eur Heart J. 2019;40(47):3824-34. doi: 10.1093/eurheartj/ehz297.
21. Kim ES, Menon V. Status of Women in Cardiovascular Clinical Trials. Arterioscler Thromb Vasc Biol. 2009;29(3):279-83. doi: 10.1161/ATVBAHA.108.179796.
22. Heidari S, Babor TF, Castro P, Tort S, Curno M. Sex and Gender Equity in Research: Rationale for the SAGER Guidelines and Recommended Use. Res Integr Peer Rev. 2016;1(2):1-9. doi: 10.1186/s41073-016-0007-6.
23. Bartz D, Chitnis T, Kaiser UB, Rich-Edwards JW, Rexrode KM, Pennell PB, et al. Clinical Advances in Sex-and Gender-Informed Medicine to Improve the Health of All: A Review. JAMA Intern Med. 2020;180(4):574-83. doi: 10.1001/jamainternmed.2019.7194.

ORIGINAL ARTICLE

Gender Based Analysis of a Population Series of Patients Hospitalized with Infective Endocarditis in Portugal – How do Women and Men Compare?

Catarina Sousa,[1,2] Paulo Jorge Nogueira,[3] Fausto J. Pinto[1,4]

Centro Cardiovascular da Universidade de Lisboa (CCUL), Centro Académico de Medicina de Lisboa (CAML), Faculdade de Medicina da Universidade de Lisboa,[1] Portugal
Serviço de Cardiologia, Centro Hospitalar Barreiro Montijo (CHBM),[2] Portugal
Área Disciplinar Autónoma de Bioestatística (Laboratório de Biomatemática), Instituto Medicina Preventiva e Saúde Publica, Faculdade de Medicina da Universidade de Lisboa,[3] Portugal
Departamento do Coração e Vasos, Centro Hospitalar Universitário Lisboa Norte (CHULN),[4] Portugal

Abstract

Background: The impact of gender on the outcome of patients hospitalized with infective endocarditis (IE) is not fully understood.

Objective: To verify the association between gender and the clinical profile of patients hospitalized with IE, treatment strategies, and clinical outcomes.

Methods: This is a retrospective nationwide study of patients hospitalized with IE, based on hospital admissions between 2010 and 2018 in Portugal. Descriptive statistics were used to present variables. An inferential analysis was performed using multiple logistic regression. A 95% confidence interval and a 5% significance level were considered.

Results: In total, 3266 (43.1%) women and 4308 (56.9%) men were hospitalized with IE. The women were older (76 vs 69 years old, p<0.001), more frequently presented arterial hypertension (39.8% vs 35.4%, p<0.001) and atrial fibrillation (29.5% vs 21.2%, p<0.001), and had less cardiovascular comorbidities. Acute heart failure was more common in women (32.9 vs 26.9%, p<0.001) and acute renal failure (13.6% vs 11.7%, p<0.001) and sepsis (12.1% vs 9.1%, p<0.001), in men. Women were less likely to undergo cardiac surgery (OR 0.48 – 95%CI 0.40–0.57, p<0.001) and had a higher postoperative mortality (OR 1.84, 95% CI 1.19–2.84, p=0.006). In-hospital mortality rates were comparable between genders (20.3% vs 19.6%, p=0.45).

Conclusions: Women were less likely to undergo cardiac surgery when hospitalized with IE, and the female gender was a predictor factor for postoperative mortality. Overall, in-hospital mortality was not influenced by gender. Further research is necessary to fully clarify the impact of gender on IE management and outcomes.

Keywords: Endocarditis; Gender and Health; Cardiac Surgery; Mortality.

Introduction

Cardiovascular diseases, including coronary heart disease, heart failure, and cerebrovascular disease, constitute leading causes of cardiovascular morbidity and mortality worldwide.[1] Great advances in cardiovascular prevention and management[2–4] have dramatically altered the outcome of these patients. Still, this trend has not been homogeneous between men and women. In the last decades, a growing awareness of the similarities and differences between men and women regarding cardiovascular function, disease burden, and epidemiology has been noted. Several initiatives issued by scientific societies have increasingly

Catarina de Sousa, MD
Cardiologist
Invited assistant of Cardiology at the Faculty of Medicine, University of Lisbon (FMUL)
Researcher at the Cardiovascular Center of the University of Lisbon (CCUL)

Mailing Address: Catarina Sousa
Av. Prof. Egas Moniz MB, 1649-028. Postal Code: 1649-028, Lisboa – Portugal.
E-mail: catarinasousacardio@gmail.com

DOI: https://doi.org/10.36660/ijcs.20210032

Manuscript received February 07, 2021; revised manuscript April 20, 2021; accepted June 02, 2021.

recognized the need for reducing the gender gap in clinical care and research.[5] Various publications have highlighted the impact of gender on several fields of cardiology such as coronary artery disease[6–8] or heart failure,[9,10] as well as in general medicine involving sepsis[11] or pneumonia.[9]

Infective endocarditis (IE) constitutes a rare condition with significant morbidity and mortality. Demographic changes, with an aging population associated with an upward trend in the implantation of prosthetic cardiac valves and cardiac devices, have justified a similar trend in the incidence of this pathology.[12–14]

The impact of gender in the clinical profile and outcome of patients with IE has been seldom approached. A higher incidence among men has been noted[15,16] in international registries. Moreover, a recent systematic review of observational series from Portugal[17] concluded that a higher prevalence of men was noted in all studies and this predominance was also noted in all surgical series (men constituted more than two-thirds of all operated patients). Still, scarce and conflicting evidence persists regarding the influence of gender on the access to cardiac surgery and fatal outcome,[18–24] being mostly based on single-center cohorts. Populational studies addressing this issue are rare,[23] yet crucial to avoid selection bias in observational studies performed in tertiary centers.

Therefore, using population-based data, the authors sought to explore the association of gender and the clinical profile of patients hospitalized with IE, access to surgical interventions, and clinical outcomes.

Methods

Study design

This is a nationwide cross-sectional study using inpatient discharge data from all public hospitals of the Portuguese National Health System (NHS) considering patients admitted with IE. A comparative analysis based on gender (women and men) was performed.

Our data source and study population were described elsewhere.[25] In brief, our data comprised hospital discharge reports including clinical information (gender, age, geographical region, hospital, date of admission and discharge, length of hospital stay, destination — home, unknown, another acute hospital, a palliative care institution or outpatient clinic, discharge against medical advice, deceased), a clinical diagnosis list (one primary diagnosis and up to nineteen secondary diagnoses), and procedures (up to twenty). The hospital discharge report used the International Classification of Diseases (ICD)-9 until 2016, and ICD-10 from then onwards. All hospitalizations of patients with an IE diagnosis at discharge (ICD-9-CM codes 421.0, 421.1, 421.9, and 424.9; ICD-10-CM I33.0, I33.9, I38, and I39) between January 1, 2010 and December 31, 2018 were considered. Each patient and hospitalization episode were linked to the first institution of hospitalization.

Variables

For each index IE hospitalization associated with valvular surgery, we identified the year of hospitalization, date of surgery (when available), presence of a cardiothoracic unit at the first hospital of admission, clinical information (gender, age, year of discharge, length of hospital stay), cardiovascular history and comorbidities (diabetes mellitus, non-rheumatic valve disease, rheumatic valve disease, affected cardiac valve, arterial hypertension, chronic kidney disease, chronic coronary artery disease, cancer, human immunodeficiency virus [HIV] infection, cardiac devices and heart valve prostheses, atrial fibrillation, chronic liver disease, chronic obstructive pulmonary disease, use of opioid drugs, congenital heart disease), microorganisms (*Staphylococcus*, *Staphylococcus aureus*, *Streptococcus*, *Enterococcus*, Gram-negative bacteria, anaerobes, fungi, *Brucella*), complications compatible with IE (heart failure, embolic stroke, ischemic stroke, transient ischemic attack, septic shock, splenic abscess, acute renal failure, acute coronary syndrome, central nervous system abscess, or meningitis), cardiac surgery, and in-hospital death using the ICD-9 and ICD-10 codes — Supplement Table S1.

Definition of postoperative and in-hospital mortality

Postoperative mortality was defined as all-cause deaths that occurred during the index hospitalization in patients who underwent cardiac surgery.

In-hospital mortality was defined as all-cause deaths that occurred during the index hospitalization in all patients hospitalized with IE.

Statistical analysis

Continuous variables were presented as means ± standard deviations if following a normal distribution; otherwise, medians and interquartile ranges were displayed. Categorical variables were expressed as frequencies and percentages. For the bivariate analysis, the comparison between continuous variables was performed through

Table 1 – Baseline characteristics of women and men hospitalized with IE in Portugal between 2010 and 2018

	Overall	Men	%	Women	%	*p*
N	7574	4308	56.9	3266	43.1	-
Age, years – median (interquartile range)	72(21)	69(22)	-	76(18)	-	**<0.001**
Cardiothoracic unit on site , number of beds (%)	3302 (43.6)	1876	43.5	1426	56.4	0.92
Length of hospital stay, days - median (interquartile range)	18(34)	22(36)	-	14(29)	-	**<0.001**
Medical history, n (%)						
Diabetes mellitus	2016 (26.6)	1116	25.9	900	27.6	0.11
Arterial hypertension	2828 (37.3)	1527	35.4	1301	39.8	**<0.001**
Atrial fibrillation	1876 (24.8)	912	21.2	964	29.5	**<0.001**
HIV	133 (1.8)	107	2.5	26	0.8	**<0.001**
CRF	887 (11.7)	515	12.0	372	11.4	0.47
CRF on hemodialysis	324 (4.3)	192	4.5	132	4.0	0.39
Non-rheumatic cardiac valve disease	1590 (21)	1044	24.2	546	16.7	**<0.001**
Rheumatic valve disease	709 (9.4)	396	9.2	313	9.6	0.58
Mitral valve disease	913 (12.1)	564	13.1	349	10.7	0.001
Aortic valve disease	903 (11.)	611	13.1	292	8.9	**<0.001**
Aortic and mitral valve disease	405 (5.3)	237	5.5	168	5.1	0.26
Right heart valve disease	447 (5.9)	243	5.6	204	6.2	0.15
Cardiac valve prosthesis	914 (12.1)	537	12.5	379	11.6	0.24
Cardiac implantable electronic devices	649 (8.6)	386	9.0	263	8.1	0.17
Coronary artery disease	970 (12.8)	606	14.1	364	11.1	**<0.001**
Previous PCI	108 (1.4)	79	1.8	29	0.9	**0.001**
Previous CABG	183 (2.4)	136	3.2	47	1.4	**<0.001**
Congenital heart disease	42 (1)	24	0.6	18	0.6	0.88
Cancer	1018 (13.4)	627	14.6	391	12.0	**0.001**
COPD	702 (9.3)	397	9.2	305	9.3	0.87
Opioid consumption	103 (1.4)	90	2.1	13	0.4	**<0.001**
Chronic liver disease	366 (4.8)	279	6.5	87	2.7	**<0.001**
Infectious agents, n (%)						
Staphylococcus	1242 (16.4)	812	18.8	430	13.2	<0.001
Staphylococcus aureus	470 (6.2)	308	7.1	162	5.0	**<0.001**
Streptococcus	1030 (13.6)	728	16.9	302	9.2	**<0.001**
Enterococcus	535 (7.1)	359	8.3	176	5.4	**<0.001**
Gram-negative bacteria	898 (11.9)	453	10.5	445	13.6	**<0.001**
Anaerobes	20 (0.3)	16	0.4	4	0.1	**0.004**
Fungi	10 (0.1)	6	0.1	4	0.1	0.99

Brucella	9 (0.1)	8	0.2	1	0.0	0.09
In-hospital complications/outcomes, n (%)						
Heart failure	2232 (29.5)	1159	26.9	1073	32.9	**<0.001**
Sepsis	968 (12.7)	586	13.6	382	11.7	**<0.01**
Ischemic stroke	706 (9.3)	403	9.4	303	9.3	0.94
Transient ischemic attack	37(0.5)	16	0.4	21	0.6	0.19
Hemorrhagic stroke	204 (2.7)	134	3.1	70	2.1	**0.01**
Systemic embolism	97 (1.3)	60	1.4	37	1.1	0.35
Splenic abscess	73 (1)	46	1.1	27	0.8	0.34
Central nervous system abscess/meningitis	91 (1.2)	60	1.4	31	0.9	0.09
Acute renal failure	819 (10.8)	523	12.1	296	9.1	**<0.001**
Acute myocardial infarction	220 (2.9)	124	2.9	96	2.9	0.89
Cardiac surgery, n (%)	937 (12.4)	705	16.4	232	7.1	**<0.001**
In-hospital death, n (%)	1513 (20)	874	20.3	639	19.6	0.45

IE: infective endocarditis; CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; CRF: chronic renal failure; HIV: human immunodeficiency virus; PCI: percutaneous coronary intervention.

an unpaired Student's t-test for normally distributed data or a Mann-Whitney test, and the comparison between categorical variables used the chi-squared test or a Fisher's exact test. The mentioned analysis was stratified by gender. Normality was verified through the Kolmogorov-Smirnov test and analysis of kurtosis and skewness values.

To assess the factors associated with in-hospital surgical intervention and in-hospital mortality, inferential analysis was performed using multiple logistic regression (a generalized linear model using binomial distribution for the error and the logit link function). The stepwise (forward) method, based on Akaike information criteria minimization, was used for the selection of variables included in the model. The adjusted odds ratio, as well as the 95% confidence interval (95% CI), were estimated for each variable included in the regression model.

All tests were 2-tailed. The level of significance was set to α=0.05.

Data were analyzed using IBM SPSS Statistics for Windows version 24 (IBM Corp., Armonk, NY, USA).

Results

Main clinical features of the overall cohort

During the study period, 3266 (43.1%) women and 4308 (56.9%) men were hospitalized with IE — see Table 1. The length of hospital stay was superior in men. Women were on average older than men and presented higher prevalence of arterial hypertension (39.8% vs 35.5%) and atrial fibrillation (29.5% vs 21.2%). In contrast, men presented higher rates of non-rheumatic valve disease, coronary artery disease, HIV, and chronic liver disease. *Staphylococcus* and specifically *Staphylococcus aureus* were the most prevalent. *Streptococcus* and *Enterococcus* were more commonly identified in men; Gram-negative agents were more frequent in women. Regarding valve disease, left heart valve involvement was more frequent in men.

In-hospital complications were similar between the two groups except for heart failure, which was more common in women, and hemorrhagic stroke, acute renal failure, and sepsis, which were more prevalent in men.

Men underwent surgery more often. Finally, the in-hospital fatal outcome was analogous between men and women. A bivariate analysis of exclusively medically managed patients revealed that women proportionally had a lower in-hospital mortality (19.4% vs 21.6%, p=0.026).

Table 2 shows a stepwise logistic regression approach to assess the in-hospital surgical management of patients hospitalized with IE. Women were less likely to undergo cardiac surgery during hospitalization (OR 0.48 – 95% CI 0.40–0.57, p<0.001).

In-hospital surgical cohort

In total, 232 (24.7%) women and 705 (75.3%) men underwent cardiac surgery during the index hospitalization for IE — Supplement Table S2.

Both groups were quite similar regarding comorbid conditions. A higher rate of atrial fibrillation was noted in women and a higher rate of malignancy , in men. Aortic valve and right heart valve disease were more prevalent in men. Regarding in-hospital complications, a higher rate of ischemic stroke was noted in men. Overall, postoperative mortality was significantly higher in women.

Postoperative mortality

Independent predictors of postoperative mortality are shown on Table 3. Female gender was an independent predictor of fatal outcome (OR 1.8, 95% CI 1.20–2.84, p=0.002). Other independent prognostic factors of in-hospital mortality in patients with IE subjected to surgery were previous coronary intervention, chronic kidney or liver disease, *Staphylococcus* or *Streptococcus* infection, acute renal failure, and sepsis. Younger patients were less likely to have a fatal outcome.

Discussion

In a contemporary populational cohort of patients hospitalized with IE in Portugal and after controlling for several risk factors, important differences were noted between women and men. Men were more prevalent, being younger and with a higher rate of comorbidities. On the other hand, women were less likely to undergo cardiac surgery during the incident hospitalization for IE, with a higher post-operative mortality rate. Even so, overall in-hospital mortality was comparable among men and women.

Our data showed a 1.3 man/woman ratio, which is in accordance with a higher prevalence of IE in men in populational studies.[12–14] The reasons for this remain speculative, but factors such as a higher valve disease prevalence in men and different hormone profiles have been previously mentioned.[19] Women were older but men presented a higher burden of comorbid conditions such as coronary artery disease, cardiac valve disease, liver failure, or malignancy. Infectious agents such as *Staphylococcus*, *Streptococcus*, or *Enterococcus* were more common in men whereas women presented a higher rate of Gram-negative agents. In-hospital complications were analogous, with women presenting a higher rate of acute heart failure while men had a higher rate of acute renal failure and sepsis. All these aspects were noted in previous gender-based studies.[18,21,23]

The male/female ratio increased to 3.0 in the surgical subgroup. Indeed, women were less likely to undergo cardiac surgery, which is a common finding with other studies.[18,19,21,23,26] Nonetheless, general indications for performing cardiac surgery in the context of IE[27] include acute heart failure, uncontrolled infection, and embolism. In this cohort, the profile of in-hospital-related complications was comparable between men and women, the latter group presenting a higher incidence of heart failure; this fails to explain the gender disparity in the access to surgical treatment among patients with IE. Additionally, men presented a higher incidence of hemorrhagic stroke, which normally delays and sometimes excludes cardiac interventions. Physician awareness[28] and other comorbidities not taken into account in this study such as frailty score,[29] dementia,[30] or neurologic sequelae could also have contributed individually to the decision to perform cardiac surgery and should be considered. Age, female gender, and endocarditis are variables included in cardiac surgery risk stratification scores such as EUROSCORE[31] or the STS[32] and the fact that women were older could have precluded cardiac surgery.

Additionally, women who underwent surgery in our study had a higher rate of fatal outcome when compared to men and constituted an independent risk factor for postoperative mortality. Demographics, comorbidities, infectious agents, and in-hospital-related complications in this surgical cohort were similar between men and women. This real-world data validates the increased surgical risk in women with IE, which is already considered in the above-mentioned risk scores. The higher surgical susceptibility of women was also found by Curlier et al.[23] and in a recent meta-analysis by Varela et al.[33] Weber et al.[22] concluded that a higher postoperative mortality rate in women was due to the presence of more comorbidities and perioperative risk factors, which was apparently not the case in the current study. This higher mortality after surgery in the female sex was also noted in other fields of cardiac surgery, such as after coronary artery bypass graft surgery.[34] Older age, a lower body surface area,[35] a higher incidence of heart failure, and referral bias[21] could also partially justify this higher surgical susceptibility.

Table 2 – Logistic regression analysis of in the characteristics of patients who underwent cardiac surgery due to IE

	Adjusted OR	95% CI		p
Gender (female)	0.481	0.403	0.573	**<0.001**
Age	0.969	0.965	0.974	**<0.001**
Non-rheumatic cardiac valve disease	3.040	2.242	4.121	**<0.001**
Arterial hypertension	1.596	1.351	1.885	**<0.001**
HIV	0.298	0.144	0.616	0.001
Cancer	0.679	0.522	0.884	0.004
Cardiac valve prostheses	1.524	1.220	1.905	**<0.001**
Cardiac devices	0.576	0.412	0.806	0.001
Chronic liver disease	0.389	0.254	0.595	**<0.001**
Mitral valve disease	2.032	1.547	2.670	**<0.001**
Aortic and mitral disease	5.425	4.161	7.071	**<0.001**
Aortic valve disease	2.181	1.637	2.905	**<0.001**
Staphylococcus	1.345	1.102	1.642	0.004
Streptococcus	1.825	1.466	2.273	**<0.001**
Enterococcus	1.544	1.164	2.047	0.003
Heart failure	1.684	1.423	1.994	**<0.001**
Hemorrhagic stroke	0.438	0.257	0.747	0.002
Systemic embolism	2.830	1.700	4.713	**<0.001**
Splenic abscess	2.039	1.145	3.632	0.016
Acute renal failure	1.508	1.210	1.879	**<0.001**

IE: infective endocarditis; CI: confidence interval; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; OR: odds ratio. Dependent variable: surgical management. Reference categories: male (gender); no (for remaining factors). Age was included as a numeric variable (covariate).

Finally, regarding in-hospital mortality, no significant differences were noted between men and women. This is similar to findings from Curlier et al.[23] It would be critical to analyze the causes of death in these patients. Actually, a recent study based on national death certificate data in Portugal[36] concluded that, in a cohort whose basic cause of death was IE, women presented a 19% higher death rate than men. Conversely, Thuny et al.[37] concluded that a high burden of comorbidities and aortic valve involvement may explain an increased death rate among women.

In our study, women differed from men in significant aspects of clinical presentation and treatment options. They were older and less likely to undergo cardiac surgery when hospitalized with IE, despite presenting less comorbid conditions and a comparable complication rate. Higher postoperative mortality, but not overall in-hospital mortality, was observed. Further research is needed to understand reasons that can explain individualized management strategies and the impact of surgery on survival in women hospitalized with IE.

Our study has several limitations. First, ICD-9 and ICD-10 codes were used to identify individual cases of IE and clinical variables on an administrative database. The authors were unable to consult the patient's electronic database to confirm the diagnosis and to identify other important variables. Therefore, diagnosis or coding errors could have occurred. Second, the authors were unable to trace patients beyond the index hospitalization and cardiac surgery could have been performed after discharge. This could lead to an underestimation of the number of cardiac surgeries performed in this cohort. Therefore, only in-hospital surgical management during

Table 3 – Logistic regression analysis of in-hospital mortality in patients who underwent cardiac surgery

	Adjusted OR	95% CI		p
Gender (female)	1.839	1.188	2.845	0.006
Age	1.062	1.043	1.082	**<0.001**
Chronic renal failure	2.694	1.475	4.920	0.001
Previous ICP	4.026	1.293	12.533	0.016
Previous CABG	8.661	2.493	30.094	0.001
Chronic liver disease	3.976	1.533	10.314	0.005
Staphylococcus	1.637	1.032	2.599	0.036
Streptococcus	0.307	0.174	0.543	**<0.001**
Hemorrhagic stroke	3.780	0.954	14.972	0.058
Acute renal failure	1.979	1.240	3.156	0.004
Sepsis	4.568	2.795	7.467	**<0.001**

CI: Confidence interval; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; OR: odds ratio.
Dependent variable: in-hospital death. For medical history conditions, infectious agents, in-hospital complications, and cardiac surgery, the reference categories were "absence/no." Age was included as a numeric variable (covariate).

the index hospitalization was assessed. Third, this is a populational study; management strategies by individual physicians and the patients' personal treatment options could thus eventually lead to a referral bias towards cardiac surgery. Fourth, variables such as microbiological subgroups, source of bacteremia (community vs healthcare-related), presence of dementia, frailty score, or a socioeconomic situation that could have further explained our findings were not available for analysis.

Conclusions

In Portugal between 2010 and 2018, hospitalization with IE occurred less frequently in women, who were older and presented fewer comorbidities. A comparable rate of in-hospital complications was observed, with a higher prevalence of acute heart failure. Regarding surgical treatment, women were less likely to undergo cardiac surgery and female gender was an independent predictor of postoperative mortality. Further research is warranted to understand the reasons behind the influence of gender on treatments and outcomes of this disease. The individualized management of IE is frequently challenging, and the influence of gender should be carefully considered together with comorbidities and complications to improve the outcome of these patients.

Acknowledgements

The authors would like to thank *Administração Central dos Sistemas de Saúde* (ACSS) for providing the clinical data. We would also like to thank Dr. Carolina Sousa for data management support.

Data availability statement

Data supporting the findings of this study are available from ACSS but restrictions apply to the availability of these data, which were used under license for the current study, thus not being publicly available. Data are however available from the authors upon reasonable request and only after permission by ACSS.

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 CAML - *Universidade Lisboa* under the protocol number 349/19. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Anonimized data was used.

Author contributions

Conception and design of the research: Sousa C, Nogueira P, Pinto F. Acquisition of data: Sousa C, Nogueira P. Analysis and interpretation of the data: Sousa C, Nogueira P. Writing of the manuscript: Sousa C. Critical revision of the manuscript for intellectual content: Sousa C, Nogueira P, Pinto F.

References

1. Nascimento BR, Brant LCC, Oliveira GMM, Malachias MVB, Reis GMA, Teixeira RA, et al. Cardiovascular Disease Epidemiology in Portuguese-Speaking Countries: data from the Global Burden of Disease, 1990 to 2016. Arq Bras Cardiol. 2018;110(6):500-11. doi: 10.5935/abc.20180098.
2. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019;50(12):e344-e418. doi: 10.1161/STR.0000000000000211.
3. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the Management of Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation: The Task Force for the Management of Acute Myocardial Infarction in Patients Presenting with ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2018;39(2):119-177. doi: 10.1093/eurheartj/ehx393.
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):2129-2200. doi: 10.1093/eurheartj/ehw128.
5. Mosca L, Barrett-Connor E, Wenger NK. Sex/gender Differences in Cardiovascular Disease Prevention: What a Difference a Decade Makes. Circulation. 2011;124(19):2145-54. doi: 10.1161/CIRCULATIONAHA.110.968792.
6. Vaccarino V, Parsons L, Every NR, Barron HV, Krumholz HM. Sex-based Differences in Early Mortality After Myocardial Infarction. National Registry of Myocardial Infarction 2 Participants. N Engl J Med. 1999;341(4):217-25. doi: 10.1056/NEJM199907223410401.
7. Maas AH, Appelman YEA. Gender Differences in Coronary Heart Disease. Neth Heart J. 2010;18(12):598-602. doi: 10.1007/s12471-010-0841-y.
8. Benamer H, Bataille S, Tafflet M, Jabre P, Dupas F, Laborne FX, et al. Longer Pre-hospital Delays and Higher Mortality in Women With STEMI: the e-MUST Registry. EuroIntervention. 2016;12(5):e542-9. doi: 10.4244/EIJV12I5A93.
9. Alsawas M, Wang Z, Murad MH, Yousufuddin M. Gender Disparities Among Hospitalised Patients with Acute Myocardial Infarction, Acute Decompensated Heart Failure or Pneumonia: Retrospective Cohort Study. BMJ Open. 2019;9(1):e022782. doi: 10.1136/bmjopen-2018-022782.
10. Mulla W, Klempfner R, Natanzon S, Mazin I, Maizels L, Abu-Much A, et al. Female Gender is Associated With a Worse Prognosis Amongst Patients Hospitalised for de-novo Acute Heart Failure. Int J Clin Pract. 2021;75(4):e13902. doi: 10.1111/ijcp.13902.
11. Sunden-Cullberg J, Nilsson A, Inghammar M. Sex-based Differences in ED Management of Critically ill Patients with Sepsis: a Nationwide Cohort Study. Intensive Care Med. 2020;46(4):727-736. doi: 10.1007/s00134-019-05910-9.
12. van den Brink FS, Swaans MJ, Hoogendijk MG, Alipour A, Kelder JC, Jaarsma W, et al. Increased Incidence of Infective Endocarditis After the 2009 European Society of Cardiology Guideline Update: a Nationwide Study in the Netherlands. Eur Heart J Qual Care Clin Outcomes. 2017;3(2):141-47. doi: 10.1093/ehjqcco/qcw039.
13. Olmos C, Vilacosta I, Fernández-Pérez C, Bernal JL, Ferrera C, García-Arribas D, et al. The Evolving Nature of Infective Endocarditis in Spain: A Population-Based Study (2003 to 2014). J Am Coll Cardiol. 2017;70(22):2795-2804. doi: 10.1016/j.jacc.2017.10.005.
14. Cresti A, Chiavarelli M, Scalese M, Nencioni C, Valentini S, Guerrini F, et al. Epidemiological and Mortality Trends in Infective Endocarditis, a 17-year Population-based Prospective Study. Cardiovasc Diagn Ther. 2017;7(1):27-35. doi: 10.21037/cdt.2016.08.09.
15. Habib G, Erba PA, Iung B, Donal E, Cosyns B, Laroche C, et al. Clinical Presentation, Aetiology and Outcome of Infective Endocarditis. Results of the ESC-EORP EURO-ENDO (European infective endocarditis) Registry: A Prospective Cohort Study. Eur Heart J. 2019;40(39):3222-32. doi: 10.1093/eurheartj/ehz620.
16. Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler VG Jr, Bayer AS, et al. Clinical Presentation, Etiology, and Outcome of Infective Endocarditis in the 21st Century: The International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med. 2009;169(5):463-73. doi: 10.1001/archinternmed.2008.603.
17. Sousa C, Ribeiro RM, Pinto FJ. The Burden of Infective Endocarditis in Portugal in the last 30 years - A systematic Review of Observational Studies. Rev Port Cardiol. 2021;40(3):205-217. doi: 10.1016/j.repc.2020.07.014.
18. Aksoy O, Meyer LT, Cabell CH, Kourany WM, Pappas PA, Sexton DJ. Gender Differences in Infective Endocarditis: pre- and co-morbid Conditions Lead to Different Management and Outcomes in Female Patients. Scand J Infect Dis. 2007;39(2):101-7. doi: 10.1080/00365540600993285.
19. Castillo JC, Anguita MP, Delgado M, Ruiz M, Mesa D, Romo E, et al. Características Clínicas y Pronóstico de la Endocarditis Infecciosa en la Mujer. Rev Esp Cardiol. 2008;61(1):36-40. doi: 10.1157/13114955.
20. Sevilla T, Revilla A, López J, Vilacosta I, Sarriá C, Gómez I, et al. Influence of Sex on Left-sided Infective Endocarditis. Rev Esp Cardiol. 2010;63(12):1497-500. doi: 10.1016/s1885-5857(10)70285-1.
21. Sambola A, Fernández-Hidalgo N, Almirante B, Roca I, González-Alujas T, Serra B, et al. Sex Differences in Native-valve Infective Endocarditis in a Single Tertiary-Care Hospital. Am J Cardiol. 2010;106(1):92-8. doi: 10.1016/j.amjcard.2010.02.019.

22. Weber C, Gassa A, Rokohl A, Sabashnikov A, Deppe AC, Eghbalzadeh K, et al. Severity of Presentation, Not Sex, Increases Risk of Surgery for Infective Endocarditis. Ann Thorac Surg. 2019;107(4):1111-17. doi: 10.1016/j.athoracsur.2018.10.033.

23. Curlier E, Hoen B, Alla F, Selton-Suty C, Schubel L, Doco-Lecompte T, et al. Relationships Between Sex, Early Valve Surgery and Mortality In Patients With Left-Sided Infective Endocarditis Analysed in a Population-based Cohort Study. Heart. 2014;100(15):1173-8. doi: 10.1136/heartjnl-2013-304916.

24. Elamragy AA, Meshaal MS, El-Kholy AA, Rizk HH. Gender Differences in Clinical Features and Complications of Infective Endocarditis: 11-year Experience of a Single Institute in Egypt. Egypt Heart J. 2020;72(1):5. doi: 10.1186/s43044-020-0039-6.

25. Sousa C, Nogueira P, Pinto FJ. Insight Into the Epidemiology of Infective Endocarditis in Portugal: A Contemporary Nationwide Study From 2010 to 2018. BMC Cardiovasc Disord. 2021;21(1):138. doi: 10.1186/s12872-021-01937-3.

26. Guiomar N, Vaz-da-Silva M, Mbala D, Sousa-Pinto B, Monteiro JP, Ponce P, et al. Cardiac Surgery in Infective Endocarditis and Predictors of In-hospital Mortality. Rev Port Cardiol. 2020;39(3):137-149. doi: 10.1016/j.repc.2019.08.009.

27. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the Management of Infective Endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 2015;36(44):3075-128. doi: 10.1093/eurheartj/ehv319.

28. Iung B, Doco-Lecompte T, Chocron S, Strady C, Delahaye F, Le Moing V, et al. Cardiac Surgery During the Acute Phase of Infective Endocarditis: Discrepancies between European Society of Cardiology Guidelines and Practices. Eur Heart J. 2016;37(10):840-8. doi: 10.1093/eurheartj/ehv650.

29. Sündermann S, Dademasch A, Praetorius J, Kempfert J, Dewey T, Falk V, et al. Comprehensive Assessment of Frailty for Elderly High-risk Patients Undergoing Cardiac Surgery. Eur J Cardiothorac Surg. 2011;39(1):33-7. doi: 10.1016/j.ejcts.2010.04.013.

30. Marques A, Cruz I, Caldeira D, Alegria S, Gomes AC, Broa AL, et al. Risk Factors for In-Hospital Mortality in Infective Endocarditis. Arq Bras Cardiol. 2020;114(1):1-8. doi: 10.36660/abc.20180194.

31. Roques F, Michel P, Goldstone AR, Nashef SA. The logistic EuroSCORE. Eur Heart J. 2003;24(9):881-2. doi: 10.1016/s0195-668x(02)00799-6.

32. Wang TK, Oh T, Voss J, Gamble G, Kang N, Pemberton J. Comparison of Contemporary Risk Scores for Predicting Outcomes After Surgery for Active Infective Endocarditis. Heart Vessels. 2015;30(2):227-34. doi: 10.1007/s00380-014-0472-0.

33. Varela Barca L, Navas Elorza E, Fernández-Hidalgo N, Moya Mur JL, Muriel García A, Fernández-Felix BM, et al. Prognostic Factors of Mortality After Surgery in Infective Endocarditis: Systematic Review And Meta-Analysis. Infection. 2019;47(6):879-895. doi: 10.1007/s15010-019-01338-x.

34. Blankstein R, Ward RP, Arnsdorf M, Jones B, Lou YB, Pine M. Female Gender is an Independent Predictor of Operative Mortality After Coronary Artery Bypass Graft Surgery: Contemporary Analysis of 31 Midwestern hospitals. Circulation. 2005;112(9 Suppl):323-7. doi: 10.1161/CIRCULATIONAHA.104.525139.

35. Ibrahim MF, Paparella D, Ivanov J, Buchanan MR, Brister SJ. Gender-related Differences in Morbidity and Mortality During Combined Valve and Coronary Surgery. J Thorac Cardiovasc Surg. 2003;126(4):959-64. doi: 10.1016/s0022-5223(03)00355-6.

36. Sousa C, Ribeiro RM, Pinto FJ. Infective Endocarditis as the Cause of Death: A Populationbased Study in Portugal, from 2002 to 2018. Acta Med Port. 2021. doi: 10.20344/amp.14609.

37. Thuny F, Giorgi R, Habachi R, Ansaldi S, Le Dolley Y, Casalta JP, et al. Excess Mortality and Morbidity in Patients Surviving Infective Endocarditis. Am Heart J. 2012;164(1):94-101. doi: 10.1016/j.ahj.2012.04.003.

*Supplemental Materials

For additional information, please click here.

Int J Cardiovasc Sci. 2021; 34(4):356-357

EDITORIAL

Surgical Mortality in Infective Endocarditis: Is There a Gender Paradox?

Daniel Seabra[1] and Cristina Gavina[1,2,3]

Hospital Pedro Hispano - ULS Matosinhos,[1] Senhora da Hora - Portugal
Department of Medicine, Faculty of Medicine, Porto University,[2] Porto - Portugal
Cardiovascular R&D Unit (UnIC), Faculty of Medicine, Porto University,[3] Porto - Portugal

Editorial referring to the article: Gender Based Analysis of a Population Series of Patients Hospitalized with Infective Endocarditis in Portugal – How do Women and Men Compare?

Cardiovascular diseases (CVD) represent a global pandemic. Although mortality due to CVD has been decreasing with improvement in diagnosis and treatment, it remains the most frequent cause of death worldwide both in men and women.[1]

Gender impacts several key aspects in CVD, such as epidemiology, pathophysiology, clinical manifestations, disease progression, response to treatment and prognosis, in areas like coronary artery disease and heart failure.[2] However, few studies analyzed the influence of gender in infectious endocarditis (IE) management and outcomes.[3,4]

IE is a relatively rare condition associated with dismal prognosis and an estimated mortality rate of 25%.[5] In recent years, there has been an epidemiological shift, affecting patients progressively older, with cardiac valvular prosthesis and devices, and in association with invasive procedures. Nevertheless, gender impact in IE is still at debate, with scarce information to elucidate its role in the disease.[6]

In the current issue of the *International Journal of Cardiovascular Sciences*, Catarina Sousa et al.[7] reviewed the impact of gender on a Portuguese National Health System (NHS) cohort of hospitalized patients with IE, characterizing their clinical profile, therapeutic strategies, and outcomes. They collected discharge data on ICD-9 and ICD-10 codes for IE from the administrative NHS database between 2010-2018, and performed a comparative analysis based on gender for several variables of interest, including age, cardiovascular history and comorbidities, infectious agents, IE complications, cardiac surgery in index hospitalization and post-operative and overall in-hospital death.

This nationwide cross-sectional study identified 7574 patients admitted for IE. There was a higher prevalence in men (56.9%), who were younger and had a higher rate of comorbidities than women, except for arterial hypertension and atrial fibrillation. Notably, additional important differences were noted between women and men, especially concerning treatment strategies. Despite the lower prevalence of comorbidities and more frequent presentation with acute heart failure, women were less likely to undergo cardiac surgery during the incident hospitalization for IE and had a higher postoperative mortality rate, independent of other prognostic factors such as sepsis or acute renal failure. Even so, overall in-hospital mortality was comparable among men and women.

Although limited by the lack of important data as the frailty score, surgical risk scores, and time to surgery, this report provided additional information about an apparent paradox of higher surgical mortality in women, already described in other cardiac surgeries.[8] In this cohort women were older, and these tend to be frailer than men. This is generally captured by

Keywords

Endocarditis; Thoracic Surgery; post-operative mortality; Sex.

Cristina Gavina, MD, PhD, FESC, FACC
Director of Cardiology and the Department of Medicine at Hospital Pedro Hispano, Matosinhos; Assistant Professor at the Faculty of Medicine of the University of Porto

Mailing Address: Cristina Gavina
R. de Dr. Eduardo Torres, s/n. Postal Code: 4450-113, Sra. da Hora – Portugal
E-mail: cristina.gavina@gmail.com

DOI: https://doi.org/10.36660/ijcs.20210182

surgical risks scores, which weren´t considered in the logistic regression analysis. An additional explanation for this intriguing question may be related to the fact that in this IE cohort males more frequently had more aggressive microbiological agents, with greater potential for severe valvular damage, favoring more frequent surgical strategy. Additionally, time to surgery can have impacted results once there are reports that early valve surgery is associated with an increased risk of death in women in the early postoperative period.[9]

The observed higher postoperative mortality in women, apparently not justified by higher burden of comorbidities as it was argued in other series,[10] should prompt additional investigation to clarify these differences. Moreover, it highlights the importance of finding better tolls for surgical risk evaluation and specific post-operative care after cardiac surgery according to gender.

References

1. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation. 2016;133(4):38-360. doi: 10.1161/CIR.0000000000000350.
2. Mauvais-Jarvis F, Merz NB, Barnes PJ, Brinton RD, Carrero JJ, DeMeo DL, et al. Sex and Gender: Modifiers of Health, Disease, and Medicine. Lancet. 2020;396(10250):565-82. doi: 10.1016/S0140-6736(20)31561-0.
3. Elamragy AA, Meshaal MS, El-Kholy AA, Rizk HH. Gender Differences in Clinical Features and Complications of Infective Endocarditis: 11-year Experience of a Single Institute in Egypt. Egypt Heart J. 2020;72(1):5. doi: 10.1186/s43044-020-0039-6.
4. Sevilla T, Revilla A, López J, Vilacosta I, Sarriá C, Gómez I, et al. Influence of Sex on Left-Sided Infective Endocarditis. Rev Esp Cardiol. 2010;63(12):1497-500. doi: 10.1016/s1885-5857(10)70285-1.
5. Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler VG Jr, Bayer AS, et al. Clinical Presentation, Etiology, and Outcome of Infective Endocarditis in the 21st Century: The International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med. 2009;169(5):463-73. doi: 10.1001/archinternmed.2008.603.
6. Habib G. Infective Endocarditis in Portugal: Changing Epidemiology but Still a Deadly Disease. Rev Port Cardiol. 2021;40(3):219-20. doi: 10.1016/j.repc.2021.01.006.
7. Sousa C, Nogueira PJ, Pinto FJ. Gender Based Analysis of a Population Series of Patients Hospitalized with Infective Endocarditis in Portugal How do Women and Men Compare?.Int J Cardiovasc Sci. 2021; 34(4):347-355. doi: https://doi.org/10.36660/ijcs.20210032.
8. Bechtel AJ, Huffmyer JL. Gender Differences in Postoperative Outcomes After Cardiac Surgery. Anesthesiol Clin. 2020;38(2):403-15. doi: 10.1016/j.anclin.2020.01.007.
9. Curlier E, Hoen B, Alla F, Selton-Suty C, Schubel L, Doco-Lecompte T, et al. Relationships between Sex, Early Valve Surgery and Mortality in Patients with Left-Sided Infective Endocarditis Analysed in a Population-Based Cohort Study. Heart. 2014;100(15):1173-8. doi: 10.1136/heartjnl-2013-304916.
10. Weber C, Gassa A, Rokohl A, Sabashnikov A, Deppe AC, Eghbalzadeh K, et al. Severity of Presentation, Not Sex, Increases Risk of Surgery for Infective Endocarditis. Ann Thorac Surg. 2019;107(4):1111-7. doi: 10.1016/j.athoracsur.2018.10.033.

Int J Cardiovasc Sci. 2021; 34(4):358-368

ORIGINAL ARTICLE

Accuracy of the Simplified Version of the Global Risk Score in Detecting Cardiovascular Risk in Women from Quilombola Communities in the State of Alagoas, Brazil

Andressa Lima Cavalcante and Haroldo da Silva Ferreira

Faculty of Nutrition of the Federal University of Alagoas, Maceió, AL – Brazil

Abstract

Background: Cardiovascular risk (CVR) monitoring is important for defining preventive actions against cardiovascular disease; this condition prevails more intensely in scenarios with less infrastructure such as African descent communities. The Framingham Risk Score (FRS) and the Global Risk Score (GRS) have been used in Brazil for CVR monitoring based on scales of points for certain risk factors. Among these, hypercholesterolemia and low high-density lipoprotein cholesterol require tests not always available in primary care. An alternative would be the simplified GRS (sGRS), in which these tests are replaced by the body mass index (kg/m^2).

Objective: To determine the accuracy of the sGRS in estimating CVR in African descent women (quilombolas) from Alagoas.

Methods: This is a cross-sectional study with a representative sample (n=1015) of women from African descent communities in Alagoas. GRS, sGRS, and FRS consisted in the sum of points obtained according to their respective scales. Receiver operating characteristic curves were used to compare the accuracy of these instruments as CVR predictors, assuming the GRS as reference. Statistical significance was assumed when $p<0.05$.

Results: The prevalence of high CVR assessed with the GRS or sGRS was similar (20.1% vs. 20.7%; $p>0.05$) and higher than that found with the FRS (4.5%; $p<0.001$). Considering the area under the curve (AUC), the sGRS had a higher discriminatory power (AUC=0.98; 95%CI: 0.98–0.99) than the FRS (AUC=0.91; 95%CI: 0.90–0.93).

Conclusion: Among black women living in regions with less infrastructure, the sGRS produced similar results to the GRS, with greater operational simplicity.

Keywords: Cardiovascular Diseases; Risk Factors; Epidemiology; African Continental Ancestry Group.

Introduction

Cardiovascular diseases (CVD) are currently the leading cause of death in Brazil and worldwide, justifying the implementation of prevention measures against this public health problem. In this sense, cardiovascular risk (CVR) monitoring allows the establishment of priorities among activities that focus on the CVD problem, assisting in the definition of practices and prognostic analyses. Several algorithms and scores are used to assess CVR, but none have been validated for the Brazilian population, even less so for the country's black population.[1,2] Therefore, there is no consensus on which procedure would be the most appropriate for this purpose.

The Brazilian Ministry of Health has recommended the Framingham Risk Score (FRS), which is intended to estimate CVR for the most severe forms of coronary artery

Andressa Lima Cavalcante, Nurse, MSc
Technique of the Center for Strategic Information and Response in Health Surveillance
State Department of Health of Alagoas

Mailing Address: Haroldo da Silva Ferreira
Av. Pilar, 550. Postal Code: 57038-430, Cruz das Almas, Maceió, AL - Brazil.
E-mail: haroldo.ufal@gmail.com

DOI: https://doi.org/10.36660/ijcs.20210068

Manuscript received March 2, 2021; revised manuscript April 27, 2021; accepted May 23, 2021.

disease (CAD). The Brazilian Society of Cardiology has recommended the Global Risk Score (GRS) to verify the 10-year risk of developing any atherosclerotic disease events.[2]

Both the FRS and GRS calculations require total cholesterol (TC) and high-density lipoprotein (HDL) data from patients, which are not always available in low-infrastructure settings. However, a simplified version of the GRS replaces these biochemical data with the body mass index (BMI). The simplified GRS (sGRS), by using measures that are easier to obtain, could thus be a better alternative for use in basic health units.[3]

All these instruments (FRS, GRS, and sGRS) derive from the Framingham Heart Study and are based on the synergism between risk factors for CVD. Therefore, their use is intended to estimate the risk of developing cardiovascular events.[3,4]

CVD affects individuals from lower-income populations more severely since they are more exposed to the different risk factors. In Brazil, the black population and particularly the quilombola population, due to institutional racism, remains historically at lower socioeconomic levels; this situation increases risks associated with CVD.[5]

Given the absence of studies on the accuracy of CVR indicators for the Brazilian population, especially for the black population, this study aimed to investigate the accuracy of the FRS and sGRS, using the GRS as reference. Additionally, we described the prevalence of risk factors for CVD in quilombola women from Alagoas.

Methods

This work is part of the project entitled II Diagnóstico de saúde e Segurança Alimentar e Nutricional das famílias das comunidades remanescentes dos quilombos do estado de Alagoas, approved by the Research Ethics Committee of Universidade Federal de Alagoas (CAAE No. 33527214.0.0000.5013).

This is a cross-sectional study; data collection was performed from April 2017 to January 2018. The prevalence of high CVR in quilombola communities was considered as the variable of interest to estimate sample size. Since no previous studies had been conducted in Alagoas, the 6% prevalence found in the state of Maranhão was used.[6] In 2015, around 6465 families were living in quilombola communities in Alagoas. Assuming that each family had one female member, 6465 women were the universe of interest of this research.[7] Using the StatCalc tool of Epi Info® 7.2.1.0 and admitting a sampling error of 1.5% for a 95% confidence interval (CI), 861 women would be required for this study. In order to compensate for possible sample losses, this number was increased by 10%, totaling 948 women.

In order to achieve this sample number, we randomly chose 34 out of the 68 existing quilombola communities. Women aged between 19 and 59 years from all households in the selected communities were eligible for the study. When there were 2 or more women in the same household, the participating woman was randomly defined. Exclusion criteria were being pregnant or in puerperium, having ingested alcoholic beverages in the last 24 hours, and presenting evident anatomical alterations.

Data collection was performed by interviewers who were properly trained for executing their activities, which occurred under constant supervision. The pilot study used to standardize procedures and test instruments took place before the fieldwork began and was conducted in a community that was not selected for the main study.

Data were collected through interviews using structured forms during home visits. Blood pressure and anthropometric measurements were also obtained. Subsequently, the women were referred to a previously defined place in the community for biochemical tests.

The following variables were obtained for the socioeconomic and demographic characterization of our sample: self-reported skin color (black/brown; other); age group (19 to 39.9; 40 to 49.9; ≥ 50 years); education (< 4; ≥ 4 years of study); marital status (single; stable relationship; widowed/separated); occupation (not working; farming; other); social class[8] (B+C; D+E; there were no families in class A); participation in the Bolsa Família Program (yes; no); and classification according to the Brazilian Food Insecurity Scale (EBIA), which classifies families as being in situations of mild, moderate, or severe food insecurity.[9]

Regarding health and lifestyle variables, the following conditions were defined: optimal blood pressure (BP), normal BP, prehypertension, and hypertension stages I, II, and III; normoglycemia, pre-diabetes mellitus, and diabetes mellitus (DM); smoking; low body weight, eutrophic, overweight, and obesity grades I, II, and III.

Optimal BP was defined by systolic blood pressure (SBP) < 120 mmHg and diastolic blood pressure (DBP) < 80 mmHg; normal BP was considered as: SBP 120–129 mmHg and DBP 80–84 mmHg; prehypertension: SBP 130–139 mmHg and/or DBP 85–89 mmHg; systemic

arterial hypertension (SAH) : SBP ≥ 140 mmHg and/or DBP ≥ 90 mmHg or when the use of antihypertensive medications was reported; stage I SAH: SBP 140–159 mmHg and/or DBP 90–99 mmHg; stage II SAH: SBP 160–179 mmHg and DBP 100–109 mmHg; stage III SAH: SBP ≥ 180 mmHg and DBP ≥ 110 mmHg.[1] SBP and DBP measurements were performed in duplicates, according to the Brazilian Guidelines of Hypertension.[1] An Omron® Hem-7200 portable equipment was used, being periodically calibrated according to the manufacturer's recommendations. If differences greater than 20 mmHg were observed between the 2 measurements, a third measurement was performed and the most discrepant result was disregarded. The mean of the 2 valid measurements was used in the analysis.

Prediabetes and DM were defined by glycated hemoglobin (HbA1c) levels between 5.7% and 6.4% and ≥ 6.5%, in that order.[10] Hypercholesterolemia, hypertriglyceridemia, and low high-density lipoprotein cholesterol (HDL-c) were determined by the following conditions (mg/dL): low-density lipoprotein (LDL) ≥ 160, triglycerides ≥ 175, and HDL < 50, respectively.[11] Dyslipidemia was designated when at least one of these lipid profile alterations was found.

In addition to the biochemical reference values, the use of hypoglycemic drugs or medications to control lipid alterations was also a criterion for defining these conditions.

TC, HDL, and HbA1c measurements were performed using a drop of blood obtained by puncturing the digital pulp, regardless of fasting.[12] These determinations were performed using an Alere Cholestech LDX® System and, in the case of HbA1C, an Alere NycoCard Reader II®, with their respective analysis cassettes.

Smoking was identified as the consumption of tobacco products in the last 3 months and assessed through the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST), validated for the Brazilian population.[13]

Nutritional status classifications were based on the BMI according to the following categories[14]: underweight (< 18.5 kg/m²); eutrophic (18.5–24.9 kg/m²); overweight (25–29.9 kg/m²); obesity grade I (30–34.9 kg/m²); obesity grade II (35–39.9 kg/m²); and obesity grade III (≥ 40 kg/m²). The weight and height of the participant were measured for calculating the BMI. Body mass was obtained using a digital scale (model 813, Seca®) with a 200 kg capacity. A portable stadiometer (model 213, Seca®) was used to measure the participants' height.

The GRS was used as reference for evaluating the accuracy of FRS and sGRS in predicting CVR. The GRS is determined by attributing points to age, waist circumference, HDL, systolic blood pressure, smoking, and DM variables, as shown in the table presented in the original publication.[3] The CVR was classified as follows: ≤ 8 points (low risk); 9 to 12 points (intermediate risk); and ≥ 13 points (high risk).[2]

The FRS was proposed in 2001 aiming to identify individuals at high risk for atherogenesis and those who were more likely to develop severe forms of CAD when the atherosclerosis process was already established.[15,16] Variables constituting the FRS are age, TC, HDL, smoking, SBP, and use of antihypertensive medication; our scores were established as presented in the original publication.[4] The FRS was classified as follows: ≤ 19 points (low risk); 20 to 22 points (intermediate risk); and ≥ 23 points (high risk).[17] This classification was proposed by the Brazilian Ministry of Health and favors specificity over sensitivity. In order to avoid this problem, in this study the sum of "intermediate risk" and "high risk" conditions was regarded as high CVR.

As mentioned previously, the sGRS is a simplification in which the procedures of the original GRS were maintained, but TC and HDL data were replaced by the BMI.[3]

Statistical analysis

Data entry was performed by independent double entry on forms generated by Epi Info® 7.2.1.0. Databases were compared to identify and correct typing errors.

A descriptive analysis was performed on the prevalence of high CVR according to the 3 protocols (GRS, sGRS, and FRS), demographic aspects, socioeconomic status, and health conditions. The measure of association was the prevalence ratio (PR) and its respective 95% CIs, calculated by the Poisson regression with robust variance adjustment.

The receiver operating characteristic (ROC) curve was used to evaluate the accuracy of sGRS and FRS as predictors of CVR using the GRS as reference. Areas under the curve (AUCs) were calculated for each of the evaluated scores using the DeLong test. The Youden index (J) was calculated using the formula J = (sensitivity + specificity) – 1 to define the best cut-off points (CPs), which considered the highest value of J. Subsequently, sensitivity and specificity were compared according to the best CPs or the originally proposed ones.

Statistical analyses were performed using Stata® 12.0 and, in all situations, statistical significance was assumed when $p < 0.05$.

Results

Our sample consisted of 1015 women. Most of them had black or brown skin, 4 or more years of study, a stable marital relationship, belonged to the lowest economic class, were in a situation of food insecurity, and were contemplated by the Bolsa Família Program. Other sociodemographic characteristics are presented in Table 1.

Table 1 also shows the prevalence of cardiovascular risk factors. A total of 22.6% women had hypertension, 25.1% had DM, and 66.8% were overweight (30.3% were obese). The most prevalent lipid alteration was low HDL, followed by hypertriglyceridemia and hypercholesterolemia.

The prevalence of high CVR according to the GRS was 20.1%, which was similar to what was found with the sGRS (20.7%) and much higher than the number observed when using the FRS (4.5%), even when this latter classification grouped "intermediate risk" cases together with the "high risk" category.

We observed a strong association between high CVR and risk factor categories (Table 2). The prevalence of this outcome showed increments ranging from 7.5 to 13.1 times in women presenting SAH stages I to III, respectively. Women with DM had a CVR almost 6 times higher than that of women without this metabolic alteration. Women with stage III obesity had an approximately 3 times higher CVR when compared with eutrophic women. Similar associations also occurred for hypercholesterolemia, hypertriglyceridemia, low HDL, and smoking. Women aged 40 to 49.9 years and those aged 50 or older had frequencies of the outcome of interest that were around 10 and 30 times higher, respectively, than that found in those under 40 years old.

As shown in Figure 1, scales resulting from the FRS and sGRS showed excellent performance in predicting cardiovascular risk (AUC > 0.9; $p < 0.001$). However, the sGRS showed a higher discriminatory power than the FRS.

Table 3 shows the best CPs found in this study, with a higher accuracy than that obtained with the originally proposed CPs, particularly for the FRS. The CP of 20, which defines intermediate- and high-risk conditions, presented a sensitivity of only 18.6%, with a very high specificity (99.0%). Using the CP of 9, established by the highest J index, sensitivity and specificity reached 98.0% and 69.0%, respectively. The prevalence of high CVR, with this change in CP, increased from 4.5% to 44.4%. Regarding the sGRS, when the CP for high CVR (CP ≥ 13.0) was changed to the one with the best performance (CP ≥ 11.0), sensitivity increased from 87.2% to 97.6%, although with a decrease in specificity (from 96.0% to 88.5%). When considering the best CP, the prevalence of high CVR increased from 20.7% to 28.8%.

Discussion

CVDs are currently the leading cause of mortality. Therefore, identifying individuals at higher risk is a critical task in public health to enable the adoption of preventive measures. It is important to have accurate and easy-to-operate tools to perform this identification. The results presented herein showed that the sGRS can be used instead of the GRS without any disadvantage. The latter is considered a more complete index because it includes biochemical data that indicate dyslipidemia, which are replaced by the BMI in the sGRS. The performance of the FRS compared to the GRS, although also satisfactory, was worse than that of the sGRS.

When the proposed CPs are used to discriminate patients at high CVR with the FRS, sensitivity is very low (despite a high specificity), which results in a high number of false negatives; this condition is not appropriate for screening CVR for elaborating preventive actions. In this perspective, the GRS should be used and, in the absence of lipid profile data, the sGRS.

Data routinely obtained in basic health units are used in the sGRS, thus this index can be widely applied even in contexts of poor infrastructure.[3] Among the information required for the sGRS, only the definition of DM is ideally performed by laboratory tests, which could be an obstacle. However, most Brazilian municipalities have implemented the Blood Glucose Self-Monitoring Program, which provides users with glucose testing supplies.[18] Moreover, the identification of diabetes can be done by self-reporting or when the patient reports the use of hypoglycemic agents.[19]

The women followed in this study belonged to quilombola communities, which comprise a social group that is specially subjected to social inequities and survive in a scenario marked by a low socioeconomic status, poor environmental conditions, and a high prevalence

Table 1 – Characterization of demographic, socioeconomic, and health conditions of women from remaining quilombola communities in the state of Alagoas, 2018.

Characteristics	Sample [a]	n (%)
Self-reported skin color	1013	-
Black + brown		922 (91.0)
Others		91 (9.0)
Education (years)	1011	-
< 4		369 (36.5)
≥ 4		642 (63.5)
Marital status	1015	-
Single		129 (12.7)
Stable relationship		799 (78.7)
Others (widowed, divorced)		87 (8.6)
Social class [b]	1015	-
B+C		59 (5.8)
D+E		956 (94.2)
Food security [c]	1001	-
Food security		260 (26.0)
Mild insecurity		324 (32.4)
Moderate insecurity		241 (24.1)
Severe insecurity		176 (17.6)
Food insecurity (all types)		741 (74.0)
Contemplated by the Bolsa Família program	1007	741 (73.6)
Main occupation	1007	-
Does not work		445 (44.2)
Family farming		335 (33.3)
Others **		227 (22.5)
Systemic arterial hypertension [d]	1015	229 (22.6)
Diabetes mellitus [e]		254 (25.1)
Excess weight (overweight + obesity; BMI ≥ 25 kg/m^2)		678 (66.8)
Hypercholesterolemia (LDL ≥ 160 mg/dL) [f]		102 (10.0)
Hypertriglyceridemia (triglycerides ≥ 175 mg/dL) [f]	1014	299 (29.5)
Low HDL (HDL < 50 mg/dL) [f]		739 (72.8)
CVR classification according to the Global Risk Score (GRS) [g]	1015	-
Low		646 (63.6)
Intermediate		165 (16.3)
High		204 (20.1)
CVR classification according to the simplified GRS [h]	1015	-
Low		652 (64.2)

Intermediate		153 (15.1)
High		210 (20.7)
CVR classification according to the Framingham Score [i]	1015	-
Low		969 (95.5)
Intermediate		42 (4.1)
High		4 (0.4)
Intermediate + High		46 (4.5)

[a] *Sample size < 1.015 due to missing information for the respective variable.*
[b] *Brazilian economic classification criteria.*[8]
[c] *Brazilian Food Insecurity Scale.*[9]
[d] *Defined by systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg or use of antihypertensive medication.*[1]
[e] *Glycated hemoglobin (HbA1c) ≥ 6.5%.*[10]
BMI: body mass index.[14]
LDL: low-density lipoprotein.
HDL: high-density lipoprotein.
CVR: cardiovascular risk.
[f] *Faludi et al. 2017.*[11]
*** Formal worker, public servant, independent worker, self-employed, retired/pensioner, student, and fisherman-gatherer .*
[g] *Précoma and Oliveira (2019).*[2]
[h] *D'Agostino et al. (2008).*[3]
[i] *Ministry of Health (2013).*[17]

of food insecurity and morbidities related to this context. These characteristics are not exclusive to the quilombola women of Alagoas (who our sample plan attempts to represent), being extended to the entire Afrodescendant Brazilian population.[20,21]

Some studies have shown a differential distribution of aggravations when comparing individuals from the quilombola population with those not from this population. Silva et al.[21] investigated the prevalence of food insecurity in 21 rural communities located in the northeast region of Brazil, 9 of which were quilombolas. A prevalence of 64.9% was observed among quilombolas and a prevalence of 42% was found in the other communities, demonstrating the greater social vulnerability of this population.

Using representative samples of quilombola (n = 1631) and non-quilombola (n = 1098) women from the state of Alagoas, Ferreira et al.[22] found that among quilombola women, overweight (50.1% vs 44.2%), body fat percentages > 33% (37.1% vs 23.3%), abdominal obesity (53.5% vs 34.3%), and hypertension (34.9% vs 11.4%) predominated in higher proportions. They concluded that quilombola women had a lower socioeconomic level and were more exposed to risk factors, which makes them more susceptible to morbidity and mortality from CVDs and justifies a prioritized attention by public policies.

Due to precarious living conditions, this population would have difficulties in adopting a healthy lifestyle. Regarding their diet, the consumption of ultra-processed foods, which are rich in sodium and poor in nutrients, may be one of the causes of a high prevalence of hypertension.[23] In our study, most women with high CVR had SAH.

Corroborating the results of previous studies, in this study we observed a high prevalence of high CVR in smokers and obese individuals, which are conditions that are potentially reversible by a timely approach in primary care.[17,24]

In addition to the risk factors traditionally involved in CVD pathogenesis, it is well known that the racial-ethnic segment investigated by this study faces institutional and personal racism, which constitutes a traumatic event that causes low self-esteem and stress that in turn affect the cardiovascular and hemodynamic conditions and may increase exposure to unhealthy behaviors.[25-28] Incidentally, a previous study with this population showed a high prevalence (65.3%) of common mental disorders.[29] In the non-quilombola population of Alagoas, this prevalence was 47.9%.[30]

In Brazil, the "Reorganization Care Plan for Hypertension and Diabetes Mellitus," implemented in 2001, targeted prevention and treatment at the primary health care level. Nevertheless, the identification of CVR

Table 2 – Prevalence of high cardiovascular risk (CVR) according to the Global Risk Score, based on risk factors for cardiovascular diseases in women (n = 1015) from remaining quilombola communities in the state of Alagoas (2018)

Variable	n (%)	High CVR (%)	PR (CI 95%)
Classification according to blood pressure (mmHg) [A]			
Optimal BP (n = 410; 40.4%) + normal BP (n = 234; 23.0%)	644 (63.4)	6.5	1
Prehypertension (SBP 130–139 and/or DBP 85–89)	142 (14.0)	21.8	3.3 (2.2–5.1)
Stage I (SBP 140–159 and/or DBP 90–99)	157 (15.5)	49.0	7.5 (5.4–10.5)
Stage II (SBP 160–179 and/or DBP 100–109)	51 (5.0)	70.6	10.8 (7.7–15.2)
Stage III (SBP ≥ 180 mmHg and/or DBP ≥ 110)	21 (2.1)	85.7	13.1 (9.4–18.5)
Total	**1015 (100.0)**	**20.1**	–
Classification according to glycated hemoglobin (HbA1c %) [B]			
Normoglycemia (< 5.7)	381 (37.6)	7.9	1
Pre-diabetes mellitus (5.7–6.4)	378 (37.3)	14.0	1.78 (1.2–2.7)
Diabetes mellitus (≥ 6.5)	254 (25.1)	46.8	5.95 (4.1–8.6)
Total	1013 (100.0)	19.9	–
Classification according to body mass index (kg/m²) [C]			
Low weight (n=20; 2.0%) + Eutrophic (n=317; 31.2%)	337 (33.2)	14.2	1
Overweight (25–29.9)	371 (36.5)	20.2	1.42 (1.1–2.0)
Obesity level I (30–34.9)	217 (21.4)	27.6	1.94 (1.4–2.7)
Obesity level II (35–39.9)	65 (6.4)	16.9	1.19 (0.6–2.2)
Obesity level III (≥ 40)	25 (2.5)	40.0	2.81 (1.62–4.8)
Dyslipidemias	798 (78.7)	22.7	2.13 (1.4–3.2)
Hypercholesterolemia (LDL ≥ 160 mg/dL)	102 (10.0)	44.1	2.53 (2.0–3.3)
Hypertriglyceridemia (triglycerides ≥ 175 mg/dL)	299 (29.5)	37.1	2.85 (2.2–3.6)
Low HDL (HDL < 50 mg/dL)	739 (72.8)	22.3	1.58 (1.1–2.2)
Smoking	225 (22.2)	45.3	3.51 (2.8–4.4)
Age group (years)			
19–39.9	577 (56.9)	2.2	1
40–49.9	251 (24.7)	27.1	10.02 (6.8–21.4)
≥ 50	187 (18.4)	65.8	29.19 (16.9–50.5)

PR: prevalence ratio
[A] Brazilian Guidelines of Arterial Hypertension.[1] BP: blood pressure. SBP or DBP: systolic blood pressure or diastolic blood pressure.
[B] Guidelines of the Brazilian Society of Diabetes 2017–2018.[10]
[C] World Health Organization, 2000.[14]

was limited to the presence of risk factors and/or target organ damage.[31] Subsequently, it was recommended that CVR assessment be carried out by means of multivariable models, adopting risk identification tools based on the Framingham study.[17,32]

Among the CVR identification methods evaluated in this study, the FRS using the CP proposed by the Ministry of Health (CP ≥ 20) showed low sensitivity (18.6%) but 99.9% specificity. As mentioned previously, this is not a good performance for a screening instrument, since it results in many false negatives. Based on the ROC curve, we observed that a CP of 9.0 would result in the highest accuracy. Using this new cutoff resulted in sensitivity and specificity values closer to those observed with the

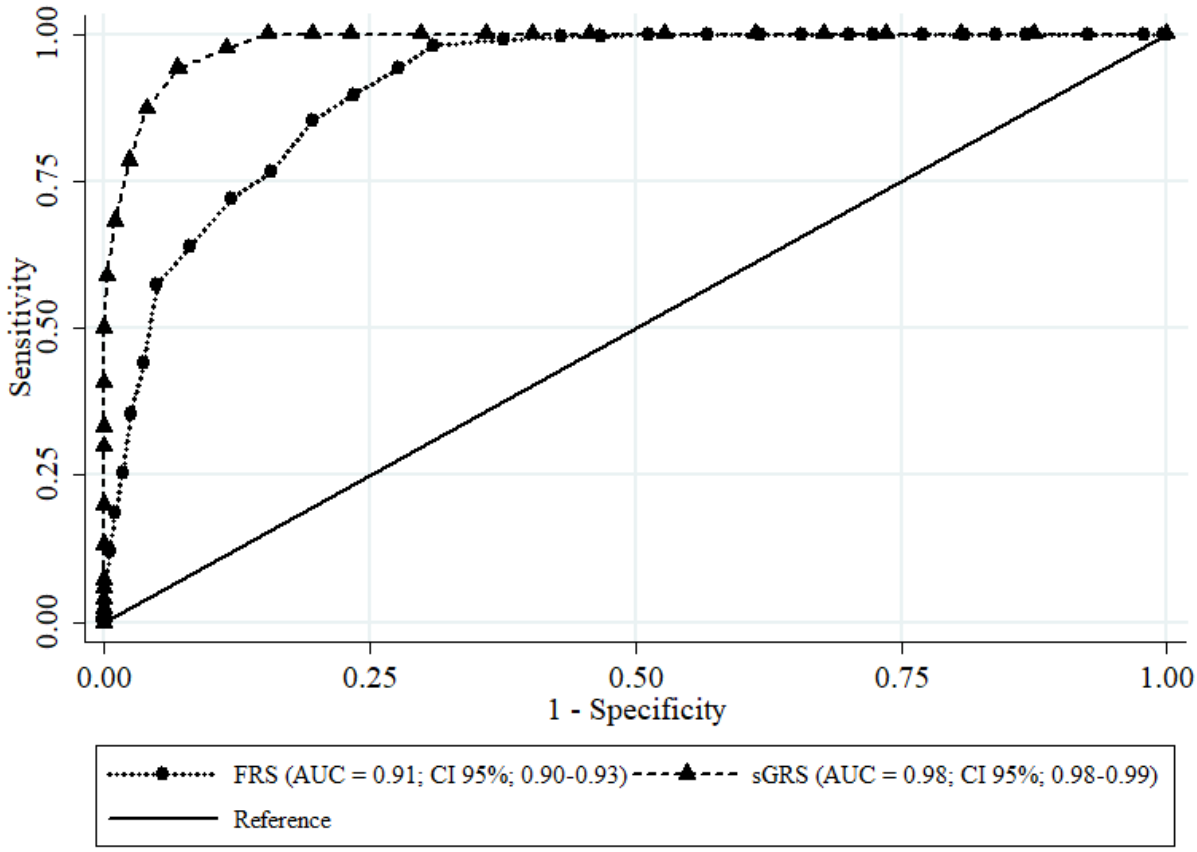


Figure 1 – Areas under the receiver operating characteristic (ROC) curve (AUCs) regarding the ability to predict high cardiovascular risk when using the simplified Global Risk Score (sGRS) or the Framingham Risk Score (FRS), with the Global Risk Score (GRS) as reference. Study with women from remaining quilombola communities in the state of Alagoas, 2018.

Table 3 – Sensitivity (S), specificity (E), and prevalence of high cardiovascular risk (high CVR) obtained according to different cut-off points (CPs) applied to the simplified Global Risk Score (sGRS) and the Framingham Risk Score, with the Global Risk Score as reference. Study with women (n = 1015) from quilombola communities in the state of Alagoas, 2018

Score	CP		S (%)	E (%)	High CVR n (%)
sGRS [a]	Original CP [a]	13.0	87.2	96.0	210 (20.7)
	Best CP [c]	11.0 [d]	97.6	88.5	292 (28.8)
Framingham Score [b]	Original CP [b]	20.0	18.6	99.0	46 (4.5)
	Best CP [c]	9.0 [e f]	98.0	69.0	451 (44.4)

[a] *D'Agostino et al. (2008).*[3];
[b] *Ministry of Health (2013).*[17]
[c] *Based on the Youden index.*
[d] *Rounded from 11.5 to 11.0 to contemplate only integer values, as in the original scale.*
[e] *Consolidating the intermediate and high CVR categories to increase sensitivity.*
[f] *Rounded from 8.5 to 9.0 to contemplate only integer values, as in the original scale.*

sGRS. This index, in turn, would have better accuracy in identifying high CVR in the studied population if the original CP (CP ≥ 13.0) were to be changed for the one defined in this study (CP ≥ 11.0) because its sensitivity would increase from 87.2% to 97.6%, although with a reduction in specificity from 96.0% to 88.5%.

In addition, regarding the low sensitivity observed when using the original cutoff point for the FRS (CP ≥ 20.0), it can be speculated that this is because this protocol was based on a subgroup of atherosclerotic diseases, requiring adjustment to assess CVR in a global scale. This reinforces the relevance of using the sGRS in primary health care. In line with our findings, a study that compared the performance of the GRS and sGRS in predicting CVR in a sample consisting of Black and White Americans[33] concluded that both indexes found similar results. Therefore, the sGRS may be an alternative for initial screenings aiming at appropriate cardiovascular health care considering cost optimization.

Therefore, the efficient management of CVR depends on the access to health services, qualified professional care, and self-care.[34] The quilombola communities face political and operational difficulties, since the nearest health services usually have inadequate infrastructure, limited and fragmented care, and few human and material resources.[35,36] Moreover, the adoption of healthy lifestyle habits also depends on the professional approach, which must consider the peculiarities of these individuals, including their beliefs.[34]

Limitations of the study

Since this was a cross-sectional study, we worked with prevalence and not incidence. It would be interesting to obtain results from longitudinal studies, in which it would be possible to obtain this parameter according to whether or not the individuals presented high CVR at the beginning of the study.

The representativeness of our results for the state of Alagoas should be regarded with some caution, since the sample calculation used the prevalence of high CVR observed in another state. However, a calculation performed a posteriori, considering our sample size (n = 1015) and the observed prevalence (20.1%), indicated a sampling error of 2.3% (0.8% higher than planned), which is a widely accepted value in population-based epidemiologic surveys.

Another limitation was the fact that we did not analyze CVR in men. This occurred because this study was part of a larger project whose operationalization involved the displacement of researchers to places of difficult access, which were distant from the state capital. Data collection took place during business hours from Monday to Friday, when most of the men in the community were working and, therefore, away from home. Consequently, our male sample was not only small, but also presented many losses, rendering the analysis unfeasible. This suggests the reproduction of this study considering male individuals, since a differential CVR seems to be present between genders.

Final considerations and conclusions

The prevention of CVD represents a public health challenge, since the development of these diseases involves the exposure to multiple risk factors, many of them closely related to living conditions and habits whose consequences arise in the long term. This is especially worrisome in the population analyzed in this study, considering the precarious conditions in which they live.

This study will contribute to the identification of the most adequate instrument for defining high CVR and classifying the individuals most exposed to the synergism between risk factors, favoring the implementation of measures to reduce CVD morbidity and mortality.

According to the results presented by this study, we conclude that the studied women presented a high prevalence of cardiovascular risk factors and that, in the absence of data on TC and HDL, the sGRS can be used without prejudice as a tool for screening those with high CVR.

Author contributions

Conception and design of the research: Cavalcante AL and Ferreira HS. Acquisition of data: Cavalcante AL and Ferreira HS. Analysis and interpretation of the data: Cavalcante AL and Ferreira HS. Statistical analysis: Cavalcante AL and Ferreira HS. Obtaining financing: Ferreira HS. Writing of the manuscript: Cavalcante AL and Ferreira HS. Critical revision of the manuscript for intellectual content: Cavalcante AL and Ferreira HS. First author master's advisor: Ferreira HS.

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 Científico e Tecnológico* - CNPq (National Council for Scientific and Technological Development), processes 442063/2014-8 e 466718/2014-4, and *Fundação de Amparo à Pesquisa do Estado de Alagoas* – FAPEAL (Research Support Foundation of the State of Alagoas), process 60030.000849/2016).

Study Association

This article is part of the thesis of master submitted by Andressa Lima Cavalcante, from *Faculdade de Nutrição da Universidade Federal de Alagoas*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Universidade Federal de Alagoas* under the protocol number CAAE nº 33527214.0.0000.5013. 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. Barroso WKS, Rodrigues CIS, Bortolotto LA, Mota-Gomes MA, Brandão AA, Feitosa ADM, et al. Brazilian Guidelines of Hypertension - 2020. Arq Bras Cardiol. 2021;116(3):516-658. doi: 10.36660/abc.20201238.
2. Précoma DB, Oliveira GMM, Simão AF, Dutra OP, Coelho OR, Izar MCO, et al. Atualização da Diretriz de Prevenção Cardiovascular da Sociedade Brasileira de Cardiologia – 2019. Arq Bras Cardiol. 2019; 113(4):787-891. doi: 10.5935/abc.20190204.
3. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General Cardiovascular Risk Profile for Use in Primary Care: The Framingham Heart Study. Circulation. 2008;117(6):743-53. doi: 10.1161/CIRCULATIONAHA.107.699579.
4. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation. 2002;106(25):3143-421.
5. Oliveira SKM, Caldeira AP. Fatores de Risco para Doenças Crônicas Não Transmissíveis em Quilombolas do Norte de Minas Gerais. Cadernos Saúde Coletiva. 2016;24:420-7. doi: 10.1590/1414-462x201600040093.
6. Barbosa MCL, Barbosa JB, Guerra LFA, Barbosa MFL, Barbosa FL, Barbosa RL, et al. Dyslipidemia and Cardiovascular Risk in Afro-Descendants: A Study of the Quilombola Communities in Maranhão, Brazil. Rev. Bras. Med. Fam. Comunidade. 2015;10(36):1-10. doi: 10.5712/rbmfc10(36)925
7. Alagoas. Secretaria de Estado do Planejamento, Gestão e Patrimônio. Estudo Sobre as Comunidades Quilombolas de Alagoas. Maceió: SEPLAG; 2015.
8. Associação Brasileira de Empresas de Pesquisa (ABEP). Critério de Classificação Econômica Brasil. Alterações na Aplicação do Critério Brasil, Válidas a Partir de 01/06/2019. São Paulo: ABEP; 2019.
9. Segall-Corrêa AM, Marin-León L, Melgar-Quiñonez H, Pérez-Escamilla R. Refinement of the Brazilian Household Food Insecurity Measurement Scale: Recommendation for a 14-item EBIA. Revista de Nutrição 2014;27(2):241-51. doi:10.1590/1415-52732014000200010.
10. Oliveira JE, Foss-Freita MC, Montenegro Junior RM, Vencio S. Diretrizes da Sociedade Brasileira de Diabetes 2017-2018. São Paulo: Editora Clannad; 2017.
11. 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. Arquivos Brasileiros de Cardiologia. 2017;109(2Supl.1):1-76. doi: 10.5935/abc.20170121.
12. Scartezini M, Ferreira CEDS, Izar MCO, Bertoluci M, Vencio S, Campana GA, et al. Positioning about the Flexibility of Fasting for Lipid Profiling. Arq Bras Cardiol. 2017;108(3):195-7. doi: 10.5935/abc.20170039.
13. Henrique IF, Micheli D, Lacerda RB, Lacerda LA, Formigoni ML. Validation of the Brazilian version of Alcohol, Smoking and Substance Involvement Screening Test (ASSIST). Rev Assoc Med Bras. 2004;50(2):199-206. doi: 10.1590/s0104-42302004000200039.
14. World Health Organization. Obesity: Preventing and Managing the Global Epidemic - Report of a WHO Consultation. Geneva: World Health Organization; 2000.
15. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of Coronary Heart Disease Using Risk Factor Categories. Circulation. 1998;97(18):1837-47. doi: 10.1161/01.cir.97.18.1837.
16. Brasil. Ministério da Saúde. Cadernos de Atenção Básica n. 14: Prevenção Clínica de Doença Cardiovascular, Cerebrovascular e Renal Crônica. Brasília: Ministério da Saúde; 2006.
17. Brasil. Ministério da Saúde. Cadernos de Atenção Básica n. 37: Estratégias para o Cuidado da Pessoa com Doença Crônica - Hipertensão Arterial. Brasília: Ministério da Saúde; 2014.
18. Matsumoto PM, Barreto ARB, Sakata KN, Siqueira YMC, Zoboli ELCP, Fracolli LA. A Educação em Saúde no Cuidado de Usuários do Programa Automonitoramento Glicêmico. Rev Esc Enferm USP. 2012;46:761-5. doi :10.1590/S0080-62342012000300031.
19. Brasil. Ministério da Saúde. Cadernos de Atenção Básica n. 36: Estratégias para o Cuidado da Pessoa com Doença Crônica - Diabetes Mellitus. Brasília (DF): Ministério da Saúde; 2013.
20. Ferreira HS, Torres ZM. Comunidade quilombola na Região Nordeste do Brasil: Saúde de Mulheres e Crianças Antes e Após sua Certificação. Revista Brasileira de Saúde Materno Infantil. 2015;15:219-29. doi:10.1590/S1519-38292015000200008.
21. Silva EKP, Medeiros DS, Martins PC, Sousa LA, Lima GP, Rêgo MAS, et al. Food Insecurity in Rural Communities in Northeast Brazil: Does Belonging to a Slave-Descendent Community Make a Difference?. Cad Saude Publica. 2017;33(4):e00005716. doi: 10.1590/0102-311X00005716.
22. Ferreira HS, Silva WO, Santos EA, Bezerra MKA, Silva BCV, Horta BL. Body Composition and Hypertension: A Comparative Study Involving Women from Maroon Communities and from the General Population of Alagoas State, Brazil. Rev Nutr. 2013;26(5):539-49. doi: 10.1590/S1415-52732013000500005.
23. Mendonça RD, Lopes AC, Pimenta AM, Gea A, Martinez-Gonzalez MA, Bes-Rastrollo M. Ultra-Processed Food Consumption and the Incidence of Hypertension in a Mediterranean Cohort: The Seguimiento Universidad de Navarra Project. Am J Hypertens. 2017;30(4):358-366. doi: 10.1093/ajh/hpw137.

24. Facchini LA, Tomasi E, Dilélio AS. Qualidade da Atenção Primária à Saúde no Brasil: Avanços, Desafios e Perspectivas. Saúde Debate. 2018;42(1):208-23. doi: 10.1590/0103-11042018S114

25. Cuevas AG, Ho T, Rodgers J, DeNufrio D, Alley L, Allen J, et al. Developmental Timing of Initial Racial Discrimination Exposure is Associated With Cardiovascular Health Conditions in Adulthood. Ethn Health. 2019:1-14. doi: 10.1080/13557858.2019.1613517.

26. Paradies Y, Ben J, Denson N, Elias A, Priest N, Pieterse A, et al. Racism as a Determinant of Health: A Systematic Review and Meta-Analysis. PLoS One. 2015;10(9):e0138511. doi: 10.1371/journal.pone.0138511.

27. Williams DR, Priest N. Racismo e Saúde: Um Corpus Crescente de Evidência Internacional. Sociologias. 2015;17(40):124-74. doi: 10.1590/15174522-017004004.

28. Freitas DA, Caballero AD, Marques AS, Hernández CIV, Antunes SLNO. Saúde e Comunidades Quilombolas: Uma Revisão da Literatura. Rev CEFAC. 2011;13(5):937-43. doi: 10.1590/S1516-18462011005000033 .

29. Neiva GS. Saúde Mental Materna e Estado Nutricional do Binômio Mãe/Filho na População Quilombola de Alagoas [dissertation]. Maceió: Universidade Federal de Alagoas; 2010.

30. Barbosa RL. Saúde Mental de Mulheres Segundo a Condição de (In) Segurança Alimentar: Estudo de Base Populacional no Estado de ALAGOAS. 2017. Maceió: Universidade Federal de Alagoas; 2018.

31. Brasil. Ministério da Saúde. Plano de Reorganização da Atenção à Hipertensão Arterial e ao Diabetes mellitus: Manual de Hipertensão Arterial e Diabetes Mellitus. Brasília (DF): Ministério da Saúde; 2001.

32. Brasil. Ministério da Saúde. Prevenção Clínica de Doenças Cardiovasculares, Cerebrovasculares e Renais. Brasília (DF): Ministério da Saúde; 2006.

33. Kariuki JK, Stuart-Shor EM, Leveille SG, Gona P, Cromwell J, Hayman LL. Validation of the nonlaboratory-based Framingham cardiovascular disease risk assessment algorithm in the Atherosclerosis Risk in Communities dataset. J Cardiovasc Med. 2017;18(12):936-45. doi: 10.2459/JCM.0000000000000583.

34. Foo KM, Sundram M, Legido-Quigley H. Facilitators and Barriers of Managing Patients With Multiple Chronic Conditions in the Community: A Qualitative Study. BMC Public Health. 2020;20(1):273. doi: 10.1186/s12889-020-8375-8.

35. Gomes KO, Reis EA, Guimarães MD, Cherchiglia ML. Use of health services by quilombo communities in southwest Bahia State, Brazil. Cad Saude Publica. 2013;29(9):1829-42. doi: 10.1590/0102-311X00151412.

36. Vieira ABD, Monteiro PS. Comunidade Quilombola: Análise do Problema Persistente do Acesso à Saúde, sob o Enfoque da Bioética de Intervenção. Saude Debate. 2013;37(99):610-18.

EDITORIAL

Cardiovascular Risk in Women from a *Quilombo* Settlement: The Effect of Aggregated Vulnerabilities

Deborah Carvalho Malta[1] and Luisa Campos Caldeira Brant[2]

Post-graduate Program in Public Health. School of Medicine. Universidade Federal de Minas Gerais,[1] Belo Horizonte, MG – Brazil
School of Medicine. Universidade Federal de Minas Gerais,[2] Belo Horizonte, MG – Brazil

Editorial referring to the article: Accuracy of the Simplified Version of the Global Risk Score in Detecting Cardiovascular Risk in Women from Quilombola Communities in the State of Alagoas, Brazil

Cardiovascular risk (CVR) is a field of great relevance with a growing number of studies throughout the country due to the magnitude of cardiovascular diseases (CVD), which have caused nearly 18 million deaths in 2016 and represent 31% of worldwide deaths.[1-3] In Brazil, CVD also lead the mortality and disability-adjusted life years (DALYs) rates,[4,5] with negative effects on the quality of life of individuals, family members, and societies.[3,5] It is noteworthy that CVD has an unequal effect on populations, with greater morbidity and mortality among low-income and least educated individuals.[6] In this context, it is important to identify the modifiable risk factors (RF) associated with CVD, such as behavioral (tobacco, alcohol, unhealthy diet, sedentarism) and metabolic RF (obesity, diabetes, hypertension, dyslipidemia); given that the risk of death from CVD attributable to metabolic RF is 74%, revealing great potential for prevention.[7,8]

CVR scores are important because evidence has shown that when RF are aggregated, they have synergistic effects on the risk of major adverse cardiovascular events (MACE).[1,9] As such, CVR scores identify high-priority individuals for specific primary preventive interventions against MACE, making them cost-effective measures that are useful in primary care.[1,9-11] Beyond the incentive for a healthy lifestyle, individuals with higher CVR should be offered statin prescriptions and be evaluated for hypertension treatment at a lower threshold.[12] A meta-analysis showed that statins can prevent 23% (relative risk [RR] 0.77 95% confidence interval [CI] 0.71–0.84) of MACE.[13] However, for primary prevention this benefit is positively correlated with CVR and non-high-density lipoprotein (HDL) cholesterol values.[13]

The study conducted by Cavalcante et al.[11] analyzed the CVR of 1015 women from Quilombo settlements in the state of Alagoas, Brazil, aged 19 to 59 years. Their work covers a gap in knowledge by collecting data from poor communities in the rural area of the Northeast region of Brazil, combining interview data with anthropometric, blood pressure, and laboratory measurements through a precise and appropriate methodology. The results indicated that 73.6% of the women were contemplated by the Bolsa Família Program, with a high prevalence of RF: hypertension (22.3%), diabetes (25.1%), and overweight and obesity (66.8%). The authors highlight that these women live "*in a scenario marked by a low socioeconomic level, precarious environmental conditions, and a high prevalence of food insecurity (74.0%); and of the morbidities related to this context*."[11]

Using the 2008 Framingham Heart Study's Global Risk Score for CVD (GRS) proposed by D'Agostino et al.,[14] they found a 20.1% prevalence of high CVR; by using the GRS as reference, the authors evaluated the accuracy of two other CVR scores: the Hard Coronary Heart Disease Framingham Risk Score,[15] which found a prevalence of high CVR of 4.5%, and the simplified Global Risk Score (sGRS), which found a prevalence of 20.7%. In conclusion, the authors emphasize

Keywords

Heart Disease Risk Factors; Health Vulnerability; Hypertension; Diabetes Mellitus; Obesity.

Deborah Carvalho Malta, MD, MSc, PhD
Associate Professor and researcher at the UFMG School of Nursing
Universidade Federal de Minas Gerais, MG - Brazil

Mailing Address: Deborah Carvalho Malta
Universidade Federal de Minas Gerais
Av. Alfredo Balena 190, Santa Efigênia. Postal Code: 30130-100, Belo Horizonte, MG - Brazil.
E-mail: dcmalta@uol.com.br

DOI: https://doi.org/10.36660/ijcs.20210163

two aspects of their work: 1) the high CVR of these socially vulnerable women living in *Quilombos*; and 2) the potential of applying the sGRS in primary care settings due to its higher discriminatory power, evaluated by the receiver operating characteristic (ROC) curve (area under the curve [AUC] = 0.98; 95%CI: 0.98–0.99), and its simplicity, as it uses the body mass index instead of total and HDL cholesterol.[11]

Regarding the first aspect, a recent study by Malta et al. (2021)[1] used laboratory data of 8953 individuals aged > 18 years from the National Health Survey (NHS) containing glycated hemoglobin, cholesterol, and blood pressure measurements. By applying the GRS, the study identified high CVR in 8.7% of women aged 30 to 74 years. The prevalence of high CVR increased with age and reflected social inequality, as it was higher in the least educated population (15.7%; 95% CI 13.5–18.3) and among Black women (14.4%; 95% CI 9.7–20.9).[1] As such, this study revealed a higher prevalence of high CV R than that reported by Cavalcante et al.,[11] probably because younger women were included in the latter.[11] In this context, we need to recognize that high CVR was found in women aged 19 to 59 years (56% < 40 years), since the strongest predictor of CVR in any risk equation is age. In fact, Cavalcante et al.[11] found that, when stratified by age, the prevalence of high CVR was 10 times higher among women aged 40–49.9 years and 30 times higher in women ≥ 50 years. It is important to note that the evaluation of the lifetime risk of CVD, in addition to the 10-year risk, should be considered for younger individuals to overcome this limitation.[16]

Regarding the second aspect, the use of the sGRS in primary care would indeed allow easier CVR assessment, which is an excellent characteristic for a screening tool and should prompt its promotion. Another suggestion by Cavalcante et al. is to use the information promptly available in primary care to calculate CVR, such as previous examinations or blood pressure measurements. Malta et al.[17] highlight how differences between CVR scores can derive from different aspects: the eligible population, predictors, and the weight of each predictor and/or outcomes (Table 1).[17] Finally, the cut-offs recommended by CVR calculators differ and are arbitrarily defined.[17] These divergences can confuse clinicians and result in misperceptions of risk and difficulties in implementing public policies, as emphasized in other international[18] and national[17] studies. In Brazil, the prevalence of individuals aged 45 to 64 years classified as intermediate or high CVR using data from the NHS had a large variation, from 2.5% (95%CI 1.8–3.3) to 44.1% (95%CI 39.7–47.3), according to which of the six scores was used.[18]

The definition of the best calculator to be implemented depends on the aim of the study. Some scores calculate only the risk of cardiovascular deaths, while others include non-fatal cardiovascular events.[13] According to Malta et al.,[17] "*the choice for which CVR calculator*

Table 1 – Characteristics of selected risk scores for the primary prevention of cardiovascular disease

	Age range	Predictors	10-year outcomes	Original cut-offs
Framingham (Global Risk Score – GRS)*	30–74	Age, sex, SBP, hypertension treatment, TC, HDL-C, diabetes, smoking	Fatal and non-fatal cardiovascular disease (coronary stroke, heart failure, intermittent claudication)	≥ 20%
Framingham (hard coronary disease)	30–79	Age, sex, SBP, hypertension treatment, TC, HDL-C, smoking**	MI (fatal or non-fatal)	≥ 20%
Pooled Cohort Equation (ACC/AHA)	40–79	Age, sex, SBP, hypertension treatment, TC, HDL-C, diabetes, smoking	Fatal coronary disease, non-fatal MI, fatal or non-fatal stroke	≥ 7.5%
WHO	40–79	Age, sex, SBP, TC, diabetes, smoking	MI or stroke (fatal or non-fatal)	≥ 20%
SCORE (High Risk – TC)	45–64	Age, sex, SBP, TC, smoking	Cardiovascular death (coronary stroke, arrhythmia, aortic aneurysm or peripheral vascular disease)	≥ 5%

SBP: systolic blood pressure; TC: total cholesterol; HDL-C: high-density lipoprotein cholesterol; MI: myocardial infarction; ACC/AHA: American College of Cardiology/American Heart Association; WHO: World Health Organization.
**In the simplified GRS (sGRS), the body mass index is used instead of TC and HDL. ** Diabetes is considered a coronary disease equivalent.*

should be used in Brazil is under debate, in the sense that there is no equation derived from a study conducted in the Brazilian population that considers the characteristics of our population, such as the racial composition, socioeconomic and geographic conditions." For that, longitudinal data evaluating MACE are needed but are not yet available in the country.[19]

Lastly, while identifying individuals with high CVR is important, population-wide strategies that promote a healthy lifestyle benefit all individuals, independently of their CVR, and are particularly relevant for socially vulnerable populations.[20] The WHO sets forth actions for the promotion of health, such as regulatory measures including the taxation of tobacco products, alcohol, and ultra-processed foods[21] and the creation of environments that render accessible and encourage healthy choices such as physical activity and healthy diets.[7,21] While mass preventive strategies are more politically challenging, particularly in a scenario of low investment in health, they need to be combined with strategies focused on individuals at high CVR to improve the cardiovascular health of all Brazilians.[22]

References

1. Malta DC, Pinheiro PC, Teixeira RA, Machado IE, Santos FMD, Ribeiro ALP. Cardiovascular Risk Estimates in Ten Years in the Brazilian Population, a Population-Based Study. Arq Bras Cardiol. 2021;116(3):423-31. doi: 10.36660/abc.20190861.
2. Santos IS. "Know the Enemy and Know Yourself". Cardiovascular Risk in the National Health Survey. Arq Bras Cardiol. 2021;116(3):432-3. doi: 10.36660/abc.20210105.
3. World Health Organization. Global Health Estimates 2016: Disease Burden by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva: World Health Organization; 2018.
4. Nascimento BR, Brant LCC, Oliveira GMM, Malachias MVB, Reis GMA, Teixeira RA, et al. Cardiovascular Disease Epidemiology in Portuguese-Speaking Countries: Data from the Global Burden of Disease, 1990 to 2016. Arq Bras Cardiol. 2018;110(6):500-11. doi: 10.5935/abc.20180098.
5. Oliveira GMM, Brant LCC, Polanczyk CA, Biolo A, Nascimento BR, Malta DC, et al. Cardiovascular Statistics - Brazil 2020. Arq Bras Cardiol. 2020;115(3):308-439. doi: 10.36660/abc.20200812.
6. Harper S, Lynch J, Smith GD. Social Determinants and the Decline of Cardiovascular Diseases: Understanding the Links. Annu Rev Public Health. 2011;32:39-69. doi: 10.1146/annurev-publhealth-031210-101234.
7. World Health Organization. Global Action Plan for the Prevention and Control of NCDs 2013-2020. Geneva: World Health Organization; 2013.
8. Global Burden of Disease Study 2019 (GBD 2019) results. Global Health Data Exchange website. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2019.
9. World Health Organization. Global NCD target prevent heart attacks and strokes through drug therapy and counselling. Genebra: World Health Organization; 2016.
10. Simão AF, Precoma DB, Andrade JP, Correa FH, Saraiva JF, Oliveira GM, et al. I Brazilian Guidelines for Cardiovascular Prevention. Arq Bras Cardiol. 2013;101(6 Suppl 2):1-63. doi: 10.5935/abc.2013S012.
11. Cavalcante AL, Ferreira HS. Accuracy of the Simplified Version of the Global Risk Score in Detecting Cardiovascular Risk in Women from Quilombola Communities in the State of Alagoas, Brazil. Int J Cardiovasc Sci. 2021; 34(4):358-368. doi:https://doi.org/10.36660/ijcs.20210068.
12. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140(11):596-646. doi: 10.1161/CIR.0000000000000678.
13. Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, et al. Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-Analysis. JAMA. 2016;316(12):1289-97. doi: 10.1001/jama.2016.13985.
14. D'Agostino RB Sr, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General Cardiovascular Risk Profile for Use in Primary Care: the Framingham Heart Study. Circulation. 2008;117(6):743-53. doi: 10.1161/CIRCULATIONAHA.107.699579.
15. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-97. doi: 10.1001/jama.285.19.2486.
16. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, et al. Prediction of Lifetime Risk for Cardiovascular Disease by Risk Factor Burden at 50 Years of Age. Circulation. 2006;113(6):791-8. doi: 10.1161/CIRCULATIONAHA.105.548206.
17. Malta DC, Pinheiro PC, Azeredo RT, Santos FM, Ribeiro ALP, Brant LCC. Prevalence of High Risk for Cardiovascular Disease Among the Brazilian Adult Population, According to Different Risk Calculators: A Comparative Study. Cien Saude Colet. 2021;26(4):1221-31. doi: 10.1590/1413-81232021264.01592021.
18. Bazo-Alvarez JC, Quispe R, Peralta F, Poterico JA, Valle GA, Burroughs M, et al. Agreement Between Cardiovascular Disease Risk Scores in Resource-Limited Settings: Evidence from 5 Peruvian Sites. Crit Pathw Cardiol. 2015;14(2):74-80. doi: 10.1097/HPC.0000000000000045.
19. Schmidt MI, Duncan BB, Mill JG, Lotufo PA, Chor D, Barreto SM, et al. Cohort Profile: Longitudinal Study of Adult Health (ELSA-Brasil). Int J Epidemiol. 2015;44(1):68-75. doi: 10.1093/ije/dyu027.
20. Rose G. Strategy of Prevention: Lessons from Cardiovascular Disease. Br Med J. 1981;282(6279):1847-51. doi: 10.1136/bmj.282.6279.
21. World Health Organization. "Best Buys" Tackling NCDs: Best buys and other recommended interventions for the prevention and control of noncommunicable diseases. Geneva: World Health Organization; 2017.
22. Brant LCC, Ribeiro ALP. Cardiovascular Health: A Global Primordial Need. Heart. 2018;104(15):1232-3. doi: 10.1136/heartjnl-2017-312562.

Int J Cardiovasc Sci. 2021; 34(4):372-382

ORIGINAL ARTICLE

Cardiovascular Risk Profile of a Young Adult Women Population Assisted in Primary Care

Tomás de Souza Mello,[1] Mariana Stutz Klen,[1] Rafael Bellotti Azevedo,[1] Fernanda Costa Barradas,[1] Luiza Araújo Nogueira,[1] Natália Rossilho Moyses Ushijima,[1] Rafael Barbosa da Silva Bica,[1] Elizabeth Silaid Muxfeldt[1,2]

Universidade Estácio de Sá, Curso de Medicina Campus Presidente Vargas, Estudo LapARC,[1] Rio de Janeiro, RJ – Brazil
Universidade Federal do Rio de Janeiro, Faculdade de Medicina,[2] Rio de Janeiro, RJ – Brazil

Abstract

Background: Although cardiovascular disease is a major cause of death among women, cardiovascular risk assessment in young women is frequently postponed due to a number of factors.

Objectives: To assess cardiovascular risk of young adult women living in one of Rio de Janeiro's Family Health Strategy geographical units in the city's central area.

Materials and Methods: populational, cross-sectional study with adults between 20 and 50 years old. Sociodemographic characteristics such as educational level and employment status were recorded. Anthropometric measurements, traditional cardiovascular risk factors, gynecological and gestational history, and selected laboratory exams were assessed. The bivariate analysis compared the baseline characteristics of the population between genders and the prevalence of cardiovascular risk factors in women according to educational level and occupation status, using non-paired Student's t-test for normal continuous variables, Mann-Whitney test for asymmetrical continuous variables, and chi-square test for categorical variables. A significance level of 5% ($p < 0.05$) was adopted.

Results: A total of 710 individuals were enrolled. In women, who comprised 59.7% of our sample, central obesity and a sedentary lifestyle were more prevalent, whereas smoking and hypertension were less observed. However, women with lower educational status had a higher prevalence of smoking and hypertension. In hypertensive women, factors such as early menopause, higher prevalence of hypertensive disorders of pregnancy and higher number of pregnancies were noticed.

Conclusion: An adverse cardiovascular risk profile in our population of young women was particularly influenced by central obesity, sedentary lifestyle, hypertensive disorders of pregnancy and lower educational status.

Keywords: Cardiovascular Diseases; Risk Factors; Young Adults; Women; Primary Health Care.

Introduction

Cardiovascular (CV) diseases are the major cause of women mortality: around 8.5 million deaths every year[1], which increases the demand for prevention strategies that take into account the particularities of its evolution.[2,3] CV risk assessment in women involves not only traditional risk factors, but specific ones (gestational complications and hormonal alterations), as well as those that have a higher impact on women's health, such as autoimmune and psychiatric diseases.[3] Regarding traditional risk factors, it must also be considered that they have different impacts on women.[4,5]

We know that women's CV risk increases in the postmenopausal period when she loses her hormonal

Natalia Rossilho Moyses Ushijima
Medical Student
Medicine Course - Campus Presidente Vargas - Universidade Estácio de Sá - RJ

Mailing Address: Elizabeth S. Muxfeldt
Rua Prof. Rodolpho Paulo Rocco, 255. Postal Code: 21941-901, Cidade Universitária, Rio de Janeiro, RJ – Brazil.
E-mail: bethmux@globo.com

DOI: https://doi.org/10.36660/ijcs.20200418

Manuscript received on December 31, 2020; reviewed on February 15, 2021; accepted on March 09, 2021.

protection. However, CV health of younger women is still less focused on the main studies: current concepts are based on findings in men and older women. The lack of specific approaches for younger women causes flaws in diagnosis, follow-up and treatment, and, consequently, worse outcomes.[4-6]

Considering the deficit of women's CV risk analysis, the objective of our study is to assess the cardiovascular risk profile of young women between 20 and 50 years old who live in the coverage area of Family Health Strategy – Lapa Health-School Center unit, in the Rio de Janeiro city center – LapARC study.

Methodology

Study design: A population, cross-sectional study from LapARC study cohort (population study of CV risk assessment) included adults between 20 and 50 years old who live in Rio de Janeiro city center, coverage area of Family Health Strategy – Lapa Health-School Center (CSE-Lapa) unit. Until now, 65% (710 individuals) of the target population (1,100 individuals) have been assessed.

***Data collection*:** Sociodemographic data were recorded, including gender, age, education (illiterate, middle school, high school, and graduate/postgraduate), and current occupation (formal or informal work, unemployed, housewife and student). The low education was defined as middle school, and we have considered unemployed, stay-at-home and student as people outside the labor market. Weight (in kg) and height (in meters) were measured using a digital scale and stadiometer to calculate body mass index (BMI) through the formula BMI = weight (kg)/height (m)^2. It was performed the measurement of waist circumference using an anthropometric tape measure. Individuals with BMI > 30 kg/m^2 were considered obese and with BMI between 25.1 and 30 kg/m^2 were considered overweight. Central obesity was defined as waist circumference > 88 cm in women and > 102 cm in men. CV risk factors were assessed by standardized questionnaires. Individuals who have smoked in the last 6 months were considered smokers, and those who have not exercised regularly for at least 150 min per week were considered sedentary. Family history of CV diseases is defined as a patient with coronary or cerebrovascular disease in 1st degree relatives (women under 65 and men under 55 years old).[7]

The diagnosis of hypertension was based on the average of two office blood pressure (BP) measurements with a digital oscillometric device (MicrolifeWatch BP03) with a cuff suitable for arm circumference, according to the Brazilian Guideline of Arterial Hypertension – 2020.[7] Patients were considered hypertensive with average office BP equal or higher than 140 x 90 mmHg or when regularly using anti-hypertensive drugs. Participants underwent Home Blood Pressure Monitoring (HBPM) (HEM-705 CP, Omron Healthcare, Kyoto, Japan), using a 7-day protocol in two morning and two afternoon measurements. The measurements of the first day were discarded and the average of the six remaining days was calculated, being considered exams with at least 12 valid measurements. The considered reference value was lower than 135x85 mmHg.[8]

Metabolic alterations were diagnosed by anamnesis (use of hypoglycemic agents and statins) and laboratory exams performed during fasting. We considered fasting glycemia between 100 and 125 mg/dl as glucose intolerance (GI) and above 126 mg/dl as diabetes mellitus (DM). To diagnose dyslipidemia, the values considered were total cholesterol above 190 mg/dl, HDL below 40 mg/dl, LDL above 130 mg/dl and triglycerides above 150 mg/dl.[9] Serum creatinine was also measured. Metabolic syndrome was defined as central obesity (waist circumference ≥ 80 cm in women or ≥ 94 cm in men) + two of the following criteria (TG ≥ 150 mg/dl, HDL-cholesterol < 40 mg/dl in men and < 50 mg/dl in women, glycemia ≥ 100 mg/dl and systolic BP ≥ 130 mmHg and diastolic BP ≥ 85 mmHg or use of anti-hypertensive drugs).[10]

Information about gynecological history was also obtained: age of menarche and (when applicable) menopause, regular use of oral or injectable contraceptive drugs, gestational history, occurrence of hypertensive disorders of pregnancy (HDP), and early menopause (before the age of 40).

Data analysis: The statistical analysis was performed using SPSS 19.0 software (SPSS, Chicago, IL, USA). Data normality was verified via histogram and Q-Q plot. Continuous variables were expressed in means and standard deviations when they presented a normal distribution and expressed in median and interquartile range in the case of asymmetrical distribution. The categorical variables were expressed in the number of individuals (n) and percentages. The bivariate analysis compares men and women through non-paired Student's t-test (normal continuous variables), Mann-Whitney test (asymmetrical continuous variables), and chi-square test (categorical variables). A significance level adopted of 5% ($p < 0.05$) was adopted. The same method was used to assess the prevalence of cardiovascular risk factors in women according to educational level and occupation.

Through multiple logistic regression, independent correlations for female sex, low education, and occupation

were assessed as dependent variables. The candidate variables for the models were age, smoking, sedentary lifestyle, obesity, central obesity, hypertension, dyslipidemia, alteration of glycemic profile (DM or GI), and metabolic syndrome. A step-by-step procedure was used to select the independent covariables ($p < 0.10$ was necessary to enter and stay in the model). The Hosmer-Lemeshow goodness-of-fit test and an estimated probability of the area under the ROC curve were used to assess calibration and discrimination of models. The results were presented as an odds ratio and confidence interval (CI) of 95%.

Ethical considerations: The study was approved by UNESA's Research Ethics Committee (number 1.389.191 in 01/15/2016 – CAAE 50605215.4.0000.5284) and the participants signed a Free and Informed Consent Term in accordance with Resolution 466/2012.

Results

A total of 710 individuals were assessed, being 424 (59.7%) women, with an average age of 36.5 ± 9.0 years. The most prevalent CV risk factors in the population were dyslipidemia (65.6%), sedentary lifestyle (44.4%), overweight (38.7%), obesity (25.2%), and hypertension (24.8%). (Table 1)

Among women, it is worth noticing the prevalence of dyslipidemia (63.9%), sedentary lifestyle (48.1%), and central obesity (48.6%). In figure 1, we observe that 77% of women presented CV risk factors and 12% of them had three or more risk factors.

When comparing both genders, women presented a higher prevalence of central obesity and sedentary lifestyle. On the other hand, they had lower levels of smoking and hypertension, with significantly lower office BP and HBPM levels. (Table 1) The main association between CV risk factors and female gender was a sedentary lifestyle, and central obesity, which presented an OR approximately 4.5 times higher than the sedentary lifestyle. (Table 2)

Current hypertension diagnosis was significantly higher not only among women with previous history of HDP (28.2% vs 8.4%), but also in those who presented early menopause (14.1% vs 4.3%). The diagnosis of hypertension was lower among nulliparous (20.5% vs 42.5%) without the influence of contraceptive use. (Table 3).

Tables 4 to 7 related education and occupation data. Comparing each educational level and occupation status with the total population of women, we observed that functionally illiterate women (10%) had higher prevalence of smoking, obesity, central obesity, hypertension, dysglycemia and metabolic syndrome, although being less sedentary. (Table 4). Low education tripled the risk of smoking and doubled the risk of hypertension, however reducing the risk of sedentary lifestyle. (Table 5) In its turn, the lack of labor market insertion reduced the risk of dyslipidemia, while formal employment reduced the risk of smoking. (Table 7).

Discussion

Despite women in pre-menopause knowingly presenting a lower CV risk, few studies assess women in this age range.[11] Our population study is one of the first studies to assess CV risk in women under the age of 50. It demonstrates that those women present higher prevalence of central obesity and are more sedentary. On the other hand, they smoke less and present lower BP levels as well as a more favorable lipid profile. In its turn, low-educated women present higher risk of smoking and hypertension, however having a lower risk of being sedentary.

Primary CV prevention in young women

Evidence shows that before menopause, higher levels of sex hormones, such as estradiol, give women a certain protection against CV diseases[12-14] through several mechanisms. However, after menopause this 'cardioprotective' effect reduces gradually and CV morbimortality becomes similar between men and women with ageing.[11,15] Despite that, there is no evidence of the benefits of hormonal therapy after menopause[16] to prevent CV diseases, although the subject is still controversial.[17]

Considering the high CV morbimortality in women and the increase of its prevalence after menopause[5,12], it is fundamental to stratify the CV risk and adopt primary prevention measures in adult women during her reproductive life.[11] In our study, most of the women between 20 and 50 years old have already presented one or more traditional CV risk factors (Figure 1). Considering young adults, most of them in the fertile age, data reinforce the importance of an individualized approach – both of each patient and of the comorbidities they present – to guarantee effective, durable benefits.

Traditional risk factors

Although there are still controversies about obesity and overweight being independent risk factors for CV diseases[18], its role in decompensating other

Table 1 – Baseline characteristics of total population, classified according to gender

Characteristics	Total population (n=710)	Female (n=424)	Male (n=286)	p-value
Age, years	36.5 ± 9.0	36.7 ± 8.9	36.1 ± 9.2	0.420
Anthropometric measures				
BMI. kg/m²	27.3 ± 5.4	27.3 ± 5.7	27.3 ± 4.9	0.932
Obesity[1], n(%)	179 (25.2)	108 (25.5)	71 (24.8)	0.930
Overweight[1], n(%)	275 (38.7)	154 (36.3)	121 (42.3)	0.116
Central obesity[2], n(%)	279 (39.3)	206 (48.6)	73 (25.5)	p < 0.001
Cardiovascular risk factors				
Family history of precocious CVD. n(%)	231 (32.5)	145 (34.2)	86 (30.1)	0.254
Physical inactivity, n(%)	315 (44.4)	204 (48.1)	111 (38.8)	0.017
Smoking, n(%)	109 (15.4)	52 (12.3)	57 (19.9)	0.008
Hypertension, n(%)	157 (24.8)	76 (19.9)	81 (32.4)	p < 0.001
Dyslipidemia, n(%)	466 (65.6)	271 (63.9)	195 (68.2)	0.260
Diabetes, n(%)	26 (3.7)	15 (3.5)	11 (3.8)	0.841
Glucose intolerance, n(%)	57 (8.0)	37 (8.7)	20 (7.0)	0.482
Metabolic Syndrome, n(%)	128 (18.0)	72 (17.0)	56 (19.6)	0.426
Blood pressure, mmHg				
Office				
Systolic BP, mmHg	122 ± 16	118 ± 15	128 ± 15	p < 0.001
Diastolic BP, mmHg	76 ± 11	75 ± 10	78 ± 11	p < 0.001
Uncontrolled BP, n(%)	97 (15.3)	36 (9.4)	61 (24.4)	p < 0.001
HBPM (n=470)		(n=291)	(n=179)	
Systolic BP, mmHg	121 ± 13	117 ± 12	126 ± 12	p < 0.001
Diastolic BP, mmHg	75 ± 10	74 ± 10	76 ± 9	0.011
Uncontrolled HBPM, n(%)	91 (19.4)	48 (16.5)	43 (24.0)	
Laboratory exams				
Glycemia, mg/dL	90 ± 15	90 ± 15	91 ± 14	0.840
Creatinine, mg/dL	0.75 ± 0.20	0.69 ± 0.17	0.84 ± 0.22	p < 0.001
Cholesterol, mg/dL	188 ± 45	191 ± 46	183 ± 43	0.069
HDL-cholesterol, mg/dL	55 ± 10	56 ± 10	53 ± 11	0.021
LDL-cholesterol, mg/dL	108 ± 40	111 ± 39	104 ± 40	0.093
Triglycerides, mg/dL	125 ± 70	123 ± 73	128 ± 64	0.511

[1] Obesity: BMI > 30 kg/m²/ Overweight: BMI between 25.1 and 30.0 kg/m²
[2] Central Obesity: women > 88 cm and men > 102
BMI: Body Mass Index; CVD: cardiovascular diseases; BP: blood pressure; HBPM: Home Blood Pressure Monitoring.
Values are averages ± SD (continuous variables) or absolute numbers and percentages (categorical variables)
The bivariate analysis compares men and women through non-paired Student's t-test (normal continuous variables and chi-square test (categorical variables).

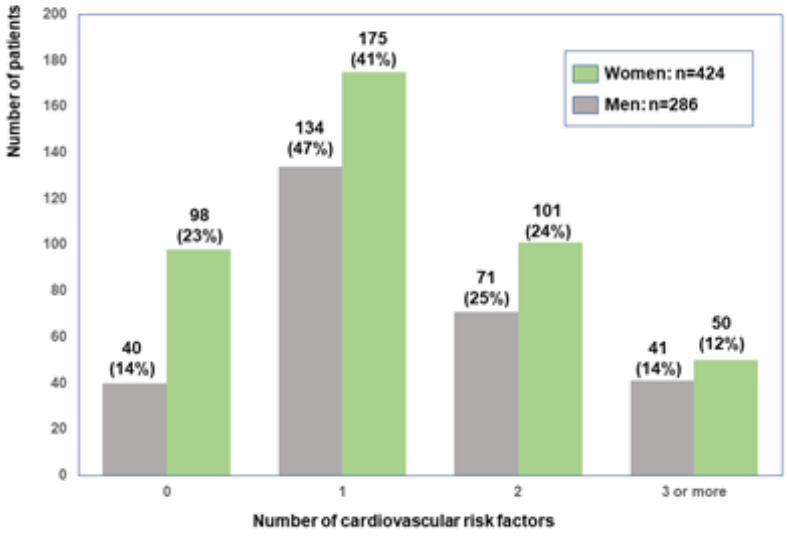


Figure 1 – Number of cardiovascular risk factors classified according to gender.

Table 2 – Logistic regression for cardiovascular risk factors in women, adjusted for age

Cardiovascular risk factors	Women OR (CI 95%)	p value
Smoking	0.56 (0.36-0.87)	0.009
Physical inactivity	1.50 (1.08-2.09)	0.015
Obesity	0.32 (0.18-0.54)	< 0.001
Central obesity	6.83 (4.06-11.50)	< 0.001
Hypertension	0.32 (0.20-0.51)	< 0.001
Dyslipidemia	0.83 (0.59-1.19)	0.317
Adverse glycemic profile	1.01 (0.59-1.62)	0.970
Metabolic Syndrome	0.95 (0.55-1.62)	0.841

Hosmer-Lemeshow goodness-of-fit test: p=0.604. Area under the ROC curve: 0.791 (95% IC 0.745-0.838)

well-established risk factors, such as dyslipidemia, hypertension and DM, is consensual.[19]

The prevalence of obesity is increasing in the Brazilian population and, among women, it is worth mentioning the increase in the pattern of central obesity, which is more related to CV risk.[20] This phenomenon seems to be related to social issues that impact women differently, such as urban violence[21], double shift work, and household chores.[22] However, it must be highlighted that indexes and cutting points to identify central obesity in Brazil are not consensual[23], and discrimination of these levels by ethnicity (white, brown and black people) seems to be needed to several CV risk factors[24], although being complex.

Nevertheless, the results of our study reflect this problem, showing similar and increased levels of obesity and overweight in both genders. Still, it draws special attention to the high prevalence of central obesity in women, which is directly related to a high CV risk. The data reinforce the need to develop public policies to prevent obesity in general and others with focus on central obesity in female patients.[3,5,19,20]

Table 3 – Risk factors related to the gynecological history for hypertension in women

	Total women (n=424)	Hypertension (n=78)	Normotension (n=346)	p-value
Menarche age, median[IQR]	13 [11-14]	12 [11.0-14.0]	13 [11.3-14.0]	0.769
Contraceptives, n(%)	126 (29.7)	20 (25.6)	108 (30.6)	0.414
Hypertensive disorders of pregnancy, n(%)	51 (12.0)	22 (28.2)	29 (8.4)	p < 0.001
Precocious menopause, n(%)	28 (6.1)	11 (14.1)	15 (4.3)	0.003
HRT, n(%)	10 (2.4)	2 (2.6)	8 (2.3)	1.00
Nulliparous, n(%)	163 (38.4)	16 (20.5)	147 (42.5)	p < 0.001
N. pregnancies, median [IQR]	2[1-3]	2 [1-3]	1 [0-2]	p < 0.001

Values are median ([interquartile range] (IQR) (continuous variables) or absolute numbers and percentages (categorical variables).
HRT, Hormone Replacement Therapy
The bivariate analysis compares normotensive and hypertensive women through Mann-Whitney test (asymmetrical continuous variables) and chi-square test (categorical variables).

Table 4 – Prevalence of cardiovascular risk factors in women according to educational level

Cardiovascular risk factors	Total population (n=424)	Functional illiterate (n=42)	Middle education (n=46)	High school/ Technical course (n=207)	Graduation/ Post-graduation (n=129)
Physical inactivity, n(%)	204 (48.1)	11 (26.2) †	19 (41.3)	100 (48.3)	74 (57.4) *
Smoking, n(%)	52 (12.3)	11 (26.2) *	10 (21.7) *	21 (10.1)	10 (7.8) *
Obesity, n(%)	107 (25.2)	17 (40.5) *	13 (28.3)	50 (24.2)	27 (20.9)
Central obesity, n(%)	206 (48.6)	29 (69.0) †	26 (56.5)	96 (46.4)	55 (42.6)
Hypertension, n(%)	78 (18.4)	16 (38.1) †	12 (26.1)	33 (15.9)	17 (13.2)
Dyslipidemia, n(%)	271 (63.9)	32 (76.2)	30 (65.2)	128 (61.8)	81 (62.8)
Adverse glycemic profile, n(%)	52 (12.3)	11 (26.2) *	3 (6.5)	23 (11.1)	15 (11.6)
Metabolic Syndrome, n(%)	72 (17.0)	17 (40.5) ‡	10 (21.7)	30 (14.5)	15 (11.6)

** p<0.05; † p<0.01; ‡ p<0.001*
The categorical variables were expressed in number of individuals (n) and percentages.
The bivariate analysis compares each educational level through chi-square test (categorical variables) in relation to total population.

Regarding dyslipidemia, although young women have a comparatively favorable profile, this tends to be reverted after menopause[24,25] with evidence that between 50 and 79 years old its prevalence becomes higher in women.[26] The criteria for drug therapy indication are the same. However, women receive it less frequently and are more prone to refuse and abandon treatment.[3,24] Thus, improvements in identifying this issue and following it up are fundamental to ameliorate the prognosis.

In our study, the extremely high prevalence of dyslipidemia in young adults (Table 1) demonstrates that this is as a primary issue of public health and reinforces the need to identify it and establish an early control. In both genders, besides drug therapy (when needed), counseling actions about healthy habits, such as balanced nutrition, weight control and regular exercises, are fundamental.[2,7,9,10,19]

The association between glycemic profile and CV risk is well established for both genders.[2,19,27] However, its

Table 5 – Logistic regression for cardiovascular risk factors and low education in women adjusted for age

Cardiovascular risk factor	Women OR (IC 95%)	p value
Smoking	3.25 (1.70-6.20)	< 0.001
Physical inactivity	0.46 (0.28-0.77)	0.003
Obesity	1.08 (0.57-2.03)	0.818
Central obesity	1.72 (0.94-3.13)	0.080
Hypertension	2.38 (1.33-4.29)	0.004
Dyslipidemia	1.29 (0.76-2.21)	0.350
Adverse glycemic profile	1.06 (0.52-2.15)	0.872
Metabolic Syndrome	1.24 (0.59-2.60)	0.566

Hosmer-Lemeshow goodness-of-fit test: p=0.632. Area under the ROC curve: 0.784 (95% IC 0.739-0.846)
Obs: Low education included those who studied until completing middle education (n=88)

Table 6 – Prevalence of cardiovascular risk factors in women according to occupation

Cardiovascular risk factors	Total population (n=424)	Formal job (n=208)	Informal job (n=65)	Unemployed (n=81)	Housewife (n=26)	Student (n=44)
Physical inactivity, n(%)	204 (48.1)	97 (46.6)	29 (44.6)	41 (50.6)	10 (38.5)	27 (61.4)*
Smoking, n(%)	52 (12.3)	19 (9.1)*	15 (23.1) †	9 (11.1)	6 (23.1)	3 (6.8)
Obesity, n(%)	107 (25.2)	57 (27.4)	16 (24.8)	23 (28.4)	8 (30.8)	3 (6.8) †
Central obesity, n(%)	206 (48.6)	106 (51.0)	32 (49.2)	40 (49.4)	15 (57.7)	13 (28.5)*
Hypertension, n(%)	78 (18.4)	37 (17.8)	13 (20.0)	16 (19.8)	8 (30.8)	4 (9.1)
Dyslipidemia, n(%)	271 (63.9)	137 (65.9)	44 (67.7)	41 (50.6) †	18 (69.2)	31 (70.5)
Adverse glycemic profile, n(%)	52 (12.3)	29 (13.9)	10 (15.4)	6 (7.4)	4 (15.4)	3 (6.8)
Metabolic Syndrome, n(%)	72 (17.0)	42 (20.2)	11 (16.9)	11 (13.6)	6 (23.1)	2 (4.5)*

** p<0.05; † p<0.01; ‡ p<0.001*
The categorical variables were expressed in the number of individuals (n) and percentages.
The bivariate analysis compares each occupation status through chi-square test (categorical variables) in relation to total population.

influence seems to be greater in women. In non-diabetic populations, CV complications are more prevalent among men in every age range, except in very elderly individuals. In patients with DM, such differences are reduced[28], suggesting that the disease counters the cardioprotective effect of female sex hormones in pre-menopause.[29] The higher relative risk of CV mortality in women with diabetes may be related, among other hypotheses, to earlier insulin resistance[3-5] and a higher average BMI when DM is diagnosed.[27]

In our study, the prevalence of GI and DM were low and similar between men and women (Table 1), possibly due to the young cohort. Despite that, it is important to remember that more unfavorable outcomes in young women will demand more attention to this group, both in monitoring and possible interventions.[2,19]

Regarding hypertension, our results were similar to those achieved in other studies in Brazil[30] and worldwide.[31,32] Data suggest that women in this age range are less prone to develop hypertension, a disease that

Table 7 – Logistic regression for cardiovascular risk factors in women out-of-work and those in formal job

Cardiovascular risk factor	Women outside labor market OR (IC 95%) (n=151)	Women with formal job OR (IC 95%) (n=208)
Smoking	1.35 (0.70-2.61)	0.53 (0.29-0.97) £
Physical inactivity	0.97 (0.62-1.51)	0.88 (0.60-1.29)
Obesity	1.34 (0.73-2.46)	1.16 (0.68-1.98)
Central obesity	1.04 (0.60-1.79)	1.13 (0.71-1.81)
Hypertension	1.41 (0.80-2.50)	0.81 (0.48-1.36)
Dyslipidemia	0.58 (0.37-0.91) £	1.20 (0.80-1.79)
Adverse glycemic profile	0.61 (0.29-1.38)	1.31 (0.72-2.39)
Metabolic Syndrome	0.76 (0.36-1.62)	1.57 (0.85-3.28)

*£ p<0.05; # p<0.01; *p<0.001*
Hosmer-Lemeshow goodness-of-fit test: p=0.594. Area under the ROC curve: 0.772 (95% IC 0.738-0.825)
Obs: Outside labor market (unemployed, housewife and student)

may be related to a higher level of female sex hormones. However, controversies about the subject persist since many other factors seem to interfere in this context, such as obesity, race/ethnicity, gynecological history, and social determinants.[30] In our study, hypertension was strongly correlated with low-educated women, even after adjusting for age (Table 5). A retrospective analysis of large cohorts involving patients of different age ranges describes earlier BP elevations in women, even when adjusting it to the remaining CV risk factors.[4,31] Our data demonstrate that hypertensive women have a higher prevalence of HDP history, early menopause and previous pregnancies. (Table 3) Thus, additional studies are needed to better establish this relationship.

Regarding risk factors related to lifestyle, our study showed a higher prevalence of sedentary lifestyle in women (Tables 1 and 2), except among those with lower education (Tables 4 and 5). This is an independent CV risk factor and regular physical activities have proved benefits to women in every age range.[33] The increased prevalence we observed was already described in the Brazilian population[34], and it signals the magnitude of this public health issue. Regarding women, it is possible to question whether these high levels may be related to social issues, such as double shift of work[22], but the actual determinants of this difference deserve further investigation.

Smoking was less frequent in women of our sample. However, the difference does not minimize its impact: the prevalence of smoking in women is growing[1] and there is evidence that smoking women have a higher risk of developing CV diseases compared to smoking men.[35] Among other outcomes, the risk of acute myocardial infarction seems to be higher[36] and general CV mortality[37] seems higher, although additional studies are needed to investigate the cause of these differences.

Risk factors specific to women

Early menopause and menarche, HDP, gestational DM and prematurity are independent CV risk factors in women.[2,3,5-7] In our study, some of these correlations become evident with significantly higher levels of hypertension in this young population among women who presented HDP, early menopause, and a higher number of pregnancies (Table 3). The same consideration highlights the importance of collecting and analyzing data still unavailable about gestational DM and prematurity in our sample. This also applies to the prevalence of polycystic ovary syndrome. Despite well studied in the literature[7,37], the association between oral contraceptives use and hypertension was not shown in our sample, possibly due to the shorter period of use.[38] Regarding the age of menarche, it was not observed different prevalence of hypertension: it is possible that it will happen to the enlargement of the sample and a longer follow-up.

Social and demographic factors

In terms of CV risk, women are particularly vulnerable to situations such as poverty, violence,[21] and absence of an adequate social protection network.[6,39] In our study, the most revealing data concerning this scenario are the association between low educational status (a strong indicator of socioeconomic standing) and the prevalence of hypertension, dysglycemia, smoking and metabolic syndrome, which confirms findings from other studies previously developed in Brazil.[40]

In our study sample, 21% of young women were classified as having a low educational status – either functionally illiterate or basic-level (up to eight years) education. Their adverse cardiovascular risk profile suggests that they need to be main targets of primary care prevention strategies. As for occupational status, only non-consistent and sporadic associations were noticed. Given the large number of women in informal employment (15% in our sample) and the ever-fluid nature of this indicator, it is clear that a longer follow-up and perhaps a larger sample will be needed to investigate these relationships.

Living in remote locations and belonging to certain ethnicities[30,39,40] (black, mixed-race and indigenous women) may also affect risk[6] and thus, in some cases, constitute confounding factors. Our sample, however, is restricted to an urban area; the location of residence does not seem to skew the results. Racial profiles, on the other hand, will have to be further addressed in future analyses, as their possible relationships with our sample's risk profiles have not yet been measured.

On the other hand, data related to the occupation did not reveal consistent correlations. It is possible that the small size of the sample and the fluid nature of this indicator makes it difficult to interpret the data – a longer follow-up of the patients will be needed to determine whether these associations with CV risk are real.

Regarding study limitations, we can highlight that until now only 65% of the target population living in the coverage area of CSE-Lapa was assessed, being therefore a smaller than expected sample. This may have prevented the achievement of statistical significance of some data. In the specific assessment of women, the lack of information about the prevalence of some specific or more impacting risk factors on women's CV health, such as polycystic ovarian syndrome, gestational diabetes, autoimmune diseases, or psychiatric diseases, as well as specific issues of domestic violence, abuse, and harassment, may have somehow created a bias in our analysis. Data concerning these parameters must be incorporated in future assessments. Similarly, comparisons between impacts of socioeconomic data, especially household income, and CV risks in men and women will also be useful to compare vulnerabilities between these groups.

Conclusions

We conclude that this population of young women presents an adverse cardiovascular and metabolic risk profile, mainly related to central obesity and sedentary lifestyle, as well as a high prevalence of dyslipidemia, and this scenario is worsened among low-educated women.

Perspectives

Primary prevention of CV diseases in young adult women has particularities that must be addressed in order to develop adequate risk assessment strategies and better interventions to avoid unfavorable outcomes. In comparison with men and older women, young women are less diagnosed, less counseled, less treated, and less followed up. In the long term, this can be translated in a higher morbidity. Thus, the point is not only to develop more studies to investigate the risk profiles of this population, but also to empower healthcare professionals to better respond to these specific demands.

LapARC study is currently enrolling participants with the initial objective to trace the CV risk profile of this young population. This cohort will be followed-up in the long term to identify the main risk factors responsible for future outcomes. This preliminary data has already identified traditional risk factors and socioeconomic determinants greatly affect these young women. Based on these data, we can later guide public policies capable of identifying particularities in the development of CV diseases in women as well as the elaboration of preventive approaches more suitable for the demands of this population.

Author contributions

Conception and design of the research: Mello TS, Bica RBS, Muxfeldt ES. Acquisition of data: Mello TS, Klen MS, Barradas FC, Nogueira LA, Ushijima NRM. Analysis and interpretation of the data: Mello TS, Azevedo RB, Bica RBS, Muxfeldt ES. Statistical analysis: Muxfeldt ES. Obtaining financing: Muxfeldt ES. Writing of the manuscript: Mello TS, Kelen MS, Barradas FC, Nogueira LA, Ushijima NRM.

Critical revision of the manuscript for intellectual content: Azevedo RB, Bica RBS, Muxfeldt ES.

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 Científico e Tecnológico* (CNPq) and *Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro* (FAPERJ).

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 Estácio de Sá* (UNESA/RJ) under the protocol number 50605215.4.0000.5284. 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. World Health Organization. (WHO) 2011. Global Atlas on Cardiovascular Disease Prevention and Control. Mendis S, Puska P, Norrving B editors. World Health Organization (in collaboration with the World Heart Federation and World Stroke Organization). Geneva; 2011.
2. Précoma DB, Oliveira GMM, Simão AF, Dutra OP, Coelho OR, Izar com, et al. Atualização da Diretriz de Prevenção Cardiovascular da Sociedade Brasileira de Cardiologia – 2019. Arq Bras Cardiol. 2019; 113(4):787-891.
3. Cho L, Davis M, Elgendy I, Epps K, Lindley KJ, Mehta PK, et al. Summary of Updated Recommendations for Primary Prevention of Cardiovascular Disease in Women: JACC State-of-the-Art Review. J Am Coll Cardiol. 2020;75(20):2602-18.
4. Ji H, Kim A, Ebinger JE, Niiranen TJ, Claggett BL, Bairey Merz CN, et al. Sex Differences in Blood Pressure Trajectories over the Life Course. JAMA Cardiol. 2020;5(3):255-62.
5. Nielsen PB, Skjøth F, Overvad TF, Larsen TB, Lip GYH. Female sex is a risk modifier rather than a risk factor for stroke in atrial fibrillation should we use a CHA2DS2-VA score rather than CHA2DS2-VASc? Circulation. 2018;137(8):832-40.
6. Norris CM, Yip CYY, Nerenberg KA, Clavel MA, Pacheco C, Foulds HJA, et al. State of the science in women's cardiovascular disease: a Canadian perspective on the influence of sex and gender. J Am Heart Assoc. 2019;9:e015634.
7. Barroso WKS, Rodrigues CIS, Bortolotto LA, Mota-Gomes MA, Brandão AA, Feitosa ADM ,et al. Diretrizes Brasileiras de Hipertensão Arterial - 2020. Arq. Bras. Cardiol. 2020; [online] ahead print. DOI: https://doi.org/10.36660/abc.20201238.
8. Nobre F, Mion Jr. D, Gomes MAM, Barbosa ECD, Rodrigues CIS, Neves MFT, et al. 6ª Diretrizes de Monitorização Ambulatorial da Pressão Arterial e 4ª Diretrizes de Monitorização Residencial da Pressão Arterial. Arq Bras Cardiol 2018; 110(5Supl.1):1-29.
9. 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(2Supl.1):1-76.
10. Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica. (ABESO). 2019. Diretrizes Brasileiras de Obesidade 2016/ ABESO. Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica. 2016. Disponível em https://abeso.org.br/wp-content/uploads/2019/12/Diretrizes-Download-Diretrizes-Brasileiras-de-Obesidade-2016.pdf
11. Wilbur J, Braun LT, Arslanian-Engoren C, Lauver DR, Halloway S. Assessing and addressing cardiovascular risk in young women. Nurs Outlook. 2018;66(3):325-8.
12. Mahajan A, Patni R, Gupta V. Menopause and cardiovascular disease. J Midlife Health. 2019;10(2):55-6.
13. Cavasin MA, Sankey SS, Yu AL, Menon S, Yang XP. Estrogen and testosterone have opposing effects on chronic cardiac remodeling and function in mice with myocardial infarction. Am J Physiol Heart Circ Physiol. 2003; 284(5):H1560-9.
14. Tomaszewski M, Charchar FJ, Maric C, Kuzniewicz R, Gola M, Grzeszczak W, et al. Association between lipid profile and circulating concentrations of estrogens in young men. Atherosclerosis. 2009; 203(1):257-62.
15. Rosano GM, Vitale C, Marazzi G, Volterrani M. Menopause and cardiovascular disease: the evidence. Climacteric. 2007;10 (Suppl 1):19-24.
16. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. for the Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA. 2002; 288(3):321-33.
17. Miller V, Naftolin F, Asthana S, Black D, Brinton E, Budoff M, et al. The Kronos Early Estrogen Prevention Study (KEEPS): what have we learned? Menopause. 2019; 26(9):1071-84.
18. Dippe Jr T, Cerci RJ. Obesity: a risk marker or an independent risk factor for coronary artery disease? Int J Cardiol Sci, 2020. 33(1):55-6..
19. Kotsis V, Tsioufis K, Antza C, Seravalle G, Coca A, Sierra C, et al. Obesity and cardiovascular risk: A call for action from the European Society of Hypertension working group of obesity, diabetes and the high-risk patient and European association for the study of obesity part B obesity-induced cardiovascular disease, early prevention strategies and future research directions. J Hypertens. 2018; 36(7):1441-55.
20. Almeida RT, Almeida MMG, Araújo T. Abdominal obesity and cardiovascular risk: performance of anthropometric indexes in women. Arq Bras Cardiol, 2009. 92(5):375-80.
21. Chaparro MP, Pina MF, Cardoso L, Santos SM, Barreto SM, Gonçalves LG, et al. The association between the neighborhood social environment and obesity in Brazil: a cross-sectional analysis of the ELSA-Brasil study. BMJ Open, 2019. 9:e026800.
22. Pinto KA, Griep RH, Rotenberg L, Almeida MCC, Barreto RS, Aquino EML. Gender, time use and overweight and obesity in adults: results of the Brazilian longitudinal study of adult health (ELSA-Brasil). PLoS ONE. 2018. 13(3):e0194190.
23. Eickemberg M, Amorim LDAF, Almeida MCC, Pitanga FJG, Aquino EML, Fonseca MJM, et al. Abdominal obesity in ELSA-Brasil (Brazil's Longitudinal Study of Adult Health): construction of a latent gold standard and evaluation of the accuracy of diagnostic indicators. Cienc Saude Colet. 2020. 25(8):2985-98.

24. Santos RD, Bensenor IM, Pereira AC, Lotufo PA. Dyslipidemia according to gender and race: The Brazilian Longitudinal Study of Adult Health (ELSA-Brasil). J Clin Lipidol. 2016;10(6):1362-8.

25. Wang X, Magkos F, Mittendorfer B. Sex differences in lipid and lipoprotein metabolism: it's not just about sex hormones. J Clin Endocrinol Metab. 2011; 96(4):885-93.

26. Peters SAE, Muntner P, Woodward M. Sex Differences in the Prevalence of, and Trends in, Cardiovascular Risk Factors, Treatment, and Control in the United States, 2001 to 2016. Circulation. 2019;139(8):1025–35.

27. Huebschmann AG, Huxley RR, Kohrt WM, Zeitler P, Regensteiner JG, Reusch JEB. Sex differences in the burden of type 2 diabetes and cardiovascular risk across the life course. Diabetologia. 2019; 62(10):1761-72.

28. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. Lancet. 2014; 383(9933):1973-80.

29. Sillars A, Ho FK, Pell GP, Gill JMR, Sattar N, Gray S, et al. Sex differences in the association of risk factors for heart failure incidence and mortality. Heart. 2020;106(3): 203-12.

30. Alves RF, Faerstein E. Educational inequalities in hypertension: complex patterns in intersections with gender and race in Brazil. Int J Equity Health. 2016;15(1):146.

31. Wenger NK, Arnold A, Bairey Merz CN, Cooper-DeHoff RM, Ferdinand KC, Fleg JL et al. Hypertension Across a Woman's Life Cycle. J Am Coll Cardiol. 2018;71(16):1797-813.

32. Santosa A, Zhang Y, Weinehall L, Zhao G, Wang NH, Zhao Q et al. Gender differences and determinants of prevalence, awareness, treatment and control of hypertension among adults in China and Sweden. BMC Public Health. 2020; 20(1):1763.

33. Colpani V, Oppermann K, Spritzer PM. Association between habitual physical activity and lower cardiovascular risk in premenopausal, perimenopausal, and postmenopausal women: a population-based study. Menopause. 2013; 20(5):525-531.

34. Guthold R, Stevens GA, Riley LM, Bull FC. Worldwide trends in insufficient physical activity from 2001 to 2016: a pooled analysis of 358 population-based surveys with 1.9 million participants. Lancet Global Health. 2018;6: e1077-86

35. Prescott E, Hippe M, Schnohr P, Hein HO, Vestbo J. Smoking and risk of myocardial infarction in women and men: longitudinal population study. BMJ. 1998; 316: 1043-7.

36. Huxley RR, Woodward M. Cigarette smoking as a risk factor for coronary heart disease in women compared with men: a systematic review and meta-analysis of prospective cohort studies. Lancet. 2011; 378(9799):1297-305.

37. Gao Z, Chen Z, Sun A, Deng X. Gender differences in cardiovascular disease. Medicine in Novel Technology and Devices. 2019; 4:100025.

38. Liu H, Yao J, Wang W, Zhang D. Association between duration of oral contraceptive use and risk of hypertension: A meta-analysis. J Clin Hypertens (Greenwich). 2017;19(10):1032-41.

39. O'Neil A, Scovelle AJ, Milner AJ, Kavanagh A. Gender/Sex as a Social Determinant of Cardiovascular Risk. Circulation. 2018; 137(8):854-64.

40. Anand SS, Razak F, Davis AD, Jacobs R, Vuksan V, Teo K, et al. Social disadvantage and cardiovascular disease: development of an index and analysis of age, sex, and ethnicity effects. Int J Epidemiol. 2006;35:1239-45.

ORIGINAL ARTICLE

Exercise Testing, Family History, and Subclinical Atherosclerosis Markers for Cardiovascular Risk Reclassification in Middle-Aged Women

Ricardo Quental Coutinho,[1] Ulisses Ramos Montarroyos,[1] Isly Maria Lucena de Barros,[1] Maria José Bezerra Guimarães,[1] Ana Paula Dornelas Leão,[1] Laura Olinda Bregieiro Fernandes Costa,[1] Ana Kelley de Lima Medeiros,[1] Maria de Fátima Monteiro,[1] Moacir de Novaes Lima Ferreira,[1] William Azem Chalela,[2] Rodrigo Pinto Pedrosa[1]

Universidade de Pernambuco,[1] Recife, PE – Brazil
Universidade de São Paulo,[2] São Paulo, SP – Brazil

Abstract

Background: Cardiovascular diseases are the main cause of death in women and the accuracy of currently available risk scores is questionable.

Objective: To reclassify the risk estimated by the Framingham Risk Score (FRS) in asymptomatic middle-aged women by incorporating family history, exercise testing variables, and subclinical atherosclerosis markers.

Methods: This cross-sectional study included 509 women (age range, 46-65 years) without cardiovascular symptoms. Those at low or intermediate risk by the FRS were reclassified to a higher level considering premature family history of acute myocardial infarction and/or sudden death; four variables from exercise testing; and two variables related to subclinical atherosclerosis markers. The homogeneity of these variables according to the FRS was verified by Pearson chi-square test ($p<0.05$).

Results: According to the FRS, 80.2%, 6.2%, and 13.6% of the women were classified as low (<5%), intermediate (5-10%), and high (>10%) risks, respectively. The intermediate-risk stratum showed the highest increase (from 6.2% to 33.3%) with addition of family history; followed by addition of chronotropic index <80% (to 24.2%); functional capacity <85% (22.2%), coronary calcium score >0 (20.6%); decreased one-minute heart rate recovery ≤12 bpm (15.2%); carotid intima-media thickness >1 mm and/or carotid plaque (13.8%) and ST-segment depression (9.0%). The high-risk stratum increased to 14.4% with the addition of reduced heart rate recovery and to 17.1% with the coronary calcium score.

Conclusion: Incorporation of premature family history of cardiovascular events, exercise testing abnormal parameters, and subclinical atherosclerosis markers into the FRS led to risk reclassification in 3.0-29.7% of asymptomatic middle-aged women, mainly by an increase from low to intermediate risk.

Keywords: Exercise Test; Heredity; Atherosclerosis; Women; Middle Aged; Estrogens; Risk Factor; Obesity; Hypertension; Myocardial Infarction; Sudden death.

Introduction

In middle-aged women, estrogen deficiency and the high prevalence of traditional risk factors such as obesity, sedentary behavior and hypertension can cause significant changes in the cardiovascular risk profile.[1,2] Although approximately 90% of these women are classified

Isly Lucena, MD, PhD
Medical assistant of the Clinic Coronary Unit - Cardiac Emergency Hospital of Pernambuco (PROCAPE-UPE)

Mailing Address: Ricardo Coutinho
Rua Arnóbio Marques, 310. Postal Code: 50100-030, Santo Amaro, Recife, PE – Brazil.
E-mail: ricardo.coutinho@upe.br

DOI: https://doi.org/10.36660/ijcs.20200414

Manuscript received on December 28, 2020; reviewed on February 12, 2021; accepted on March 09, 2021.

as "low risk" based on the Framingham Risk Score (FRS), events such as acute myocardial infarction and sudden death are common in this group,[3,4] suggesting that traditional cardiovascular risk scores may not be accurate.[3,5-7] Thus, variables not included in the traditional scores, such as a premature family history of cardiovascular events,[3,4] exercise testing variables,[4,5-10] and subclinical atherosclerosis markers have been considered for risk reclassification in women.[8,9,11,12] In addition, a history of infarction or death from cardiovascular disease in first-degree male relatives before 55 years of age and female relatives before 60 years of age has been considered in this regard.[1,10,13] The prevalence of subclinical atherosclerosis is found to be high in women with a family history of cardiovascular events, even in those at low risk according to the FRS.[12,13]

Among the markers of subclinical atherosclerosis, coronary calcium score has been of increasing interest, especially in asymptomatic individuals deemed to be at intermediate risk by the FRS,[3,14,15] since it is able to detect coronary calcifications that correlate with disease extent and cardiovascular events.[16,17] Another marker of subclinical atherosclerosis, carotid intima-media thickness (CIMT), assessed by ultrasonography, is associated with the presence and extent of disease in both men and women, and a predictor of myocardial infarction and stroke.[11,18,19]

Exercise testing, a non-invasive functional method established in the field of cardiology, is not only of high diagnostic value, but also of prognostic value, including in asymptomatic women.[20-23] In this sense, valuable information can be obtained regarding the prediction of cardiovascular risk when exercise parameters – functional capacity, chronotropic response, chronotropic index, heart rate (HR) recovery, and ventricular ectopy after exercise – are assessed.[24-30]

Studies have demonstrated the prognostic role of imaging and functional tests, alone but especially in combination, to identify which women are at greatest risk for cardiovascular events.[31-33] Thus, markers of subclinical atherosclerosis and exercise testing variables may contribute to the adoption of earlier and more effective preventive measures,[8,9,18,33,34] especially in those initially classified as low or intermediate risk by the FRS.

In this context, the purpose of this study was to reclassify the risk estimated by the FRS in asymptomatic middle-aged women with the incorporation of a premature family history of cardiovascular events, exercise testing variables, and subclinical atherosclerosis markers.

Materials and methods

Study design and participants

It was a cross-sectional study with women aged 46-65 years selected by convenience sampling at two women's health outpatient clinics. The sample studied (n=509) was greater than the calculated sample size (n=384), obtained by the method recommended when the frequency of the event in an infinite population is unknown.[35] For sample calculation, we used: estimated frequency in the population (proportion of women whose cardiovascular risk was assessed by the two methods) equal to 50%, using the maximum possible variability; 95% confidence interval; 5% margin of error; and infinite population size. The following exclusion criteria were adopted: history or clinical evidence of cardiovascular disease, except hypertension; diagnosis of liver or kidney disease; use of corticosteroids or hormone replacement therapy; pregnancy; use of intrauterine device; use of hormonal contraceptives for at least one year; and contraindication to exercise testing according to the III Brazilian Society of Cardiology Guideline for Exercise Testing.[20]

Variables and data collection

Of all women participating in the study, the following data were collected – age, weight, height, smoking habit, history of diabetes and systemic arterial hypertension, use of HR-reducing medication, and history of parents and siblings (<60 years of age for female relatives and <55 years of age for male relatives) with acute myocardial infarction and/or sudden death. Measurement of blood pressure, serological tests (fasting glycemia, total cholesterol and fractions, triglycerides), exercise testing, carotid artery ultrasound (for determination of CIMT), and chest tomography (to determine the coronary calcium score) were performed.

The FRS was obtained from variables including age, total cholesterol and fractions, blood pressure, and smoking. The FRS was categorized into three strata of cardiovascular risk, low (<5%), intermediate (5-10%), and high (>10%), according to the American Heart Association[5] and the Brazilian Society of Cardiology[9] recommendations for female patients. All diabetic women were classified as "high risk".

Exercise testing was performed by the principal investigator following the symptom-limited Bruce protocol[36] (Inbramed® treadmill, using the ErgoPc® exercise testing program and a Unitec® mercury manometer). Interpretation of the exercise testing results

was made according to the parameters established by the Brazilian Society of Cardiology.[20] For calculation of the exercise testing variables considered predictors of mortality, the following formulae were used:[21,23] (a) Functional capacity = (maximum VO_2 reached × 100)/VO_2 predicted considering the predicted VO_2 = 14.7 - (0.13 × age); (b) chronotropic index = (maximum HR - resting HR) × 100/(predicted HR - resting HR). The predicted HR was considered as (220 - age) as recommended by Karnoven et al.;[37] and (c) decrease in HR recovery at 1 minute = maximum HR - HR recovery at 1 minute.

CIMT was measured by carotid artery ultrasound (12-3-MHz EnVisor Ultrasound System; Philips Ultrasound, Bothell, WA, USA) by the same technician. The average of maximum CIMT was obtained from the right and left carotid segments. CIMT values >1 mm and the presence of atheroma plaque in the carotid artery[18] were used as indicators of subclinical carotid atherosclerosis. Carotid plaque was defined as the presence of focal wall thickening at least 50% greater than the wall thickness of the surrounding vessel or as a focal region with an intima-media thickness >1.5 mm projecting to the lumen distinct from the adjacent contour.[18]

For coronary calcium score, non-contrast chest tomography with low effective radiation dose (1.7-2.5 mSv) was performed by multi-channel detector computed tomography (Philips Brilliance CT-10; Philips, Amsterdam, The Netherlands). Images were prospectively obtained using the single 20-second acquisitions of deep-inspiration breath-hold technique and synchronized with electrocardiogram to obtain 3-mm cuts from the level of the carina to the level of the diaphragm.[12,15] Coronary calcification was defined as a plaque of at least three consecutive pixels (area = 1.03 mm^2) with density ≥130 Hounsfield units (HU). The coronary calcium score was calculated according to the method described by Agatston,[38] i.e., multiplying the area of calcification in square millimeters by a factor of 1, 2, 3, or 4 depending on attenuation coefficients determined by calcium. Factor 1 was used when the coefficients were 130-199 HU; factor 2, 200-299 HU; factor 3, 300-399 HU; and factor 4, >400 HU.

Statistical analysis

Continuous variables are presented as mean and standard deviation, and categorical variables as absolute and relative frequencies. Homogeneity of the variables used for cardiovascular risk reclassification was verified by the Pearson chi-square test ($p < 0.05$).

Women classified as "low" or "intermediate" cardiovascular risk based on the FRS were reclassified to "high" risk if they had one or more of the following parameters: (a) premature family history of acute myocardial infarction and/or sudden death; (b) chronotropic index <80% or <62% if using HR-lowering medication; (c) functional capacity <85%; (d) decrease in HR recovery at 1 minute ≤12 bpm; (e) ST-segment depression; (f) CIMT >1 mm and/or presence of carotid plaque; or (g) coronary calcium score >0.

With the incorporation of premature family history of cardiovascular events, exercise test variables, and atherosclerosis markers into the FRS, the increase in cardiovascular risk corresponded to the proportion of participants who were reclassified to a higher risk level. The database was built in the Microsoft Office Access program and analysis was performed using the SPSS program (version 21.0).

Results

More than one-third of the middle-aged women participating in the study (mean age, 56.4 ± 4.8 years; body mass index, 27.8 ± 4.9 kg/m^2) had systemic arterial hypertension, dyslipidemia, and obesity (Table 1). Among them, 11.2% were diabetic and 7.7% reported smoking. Approximately 11.0% were using HR-reducing medication to control systemic arterial hypertension. In the exercise testing (Table 1), mean values of maximal HR, exercise time, and VO_2 were adequate for test interpretation.

Among the variables incorporated into the FRS for cardiovascular risk reclassification (Table 2), premature family history of acute myocardial infarction and/or sudden death was the most frequent (more than one-third of participants), followed by chronotropic index, with almost one-third of participants with values below 80% or 62% (in users of HR-lowering drugs). The lowest frequency was related to ST-segment depression, observed in 22 women (4.4%), of whom only 11 (2.2% of the total sample) had a horizontal or descending pattern (>1 mm), suggestive of myocardial ischemia. According to the FRS strata, differences ($p<0.05$) were observed only in the distribution of the chronotropic index and carotid calcium score.

As shown in Figure 1, about 6% of the women were classified as intermediate risk by the FRS. After the variables of interest were added, the percentage of women at this stratum increased, with the highest increment (to 33.3%) after the addition of premature family history of cardiovascular events, followed by low chronotropic index (24.2%) and impairment in functional capacity (22.2%) (Figure 1).

Table 1 – Characteristics of participants and exercise testing parameters

Variable	Value (n = 509)
Age group [n (%)], years	
46-55	231 (46.1%)
56-60	147 (29.3%)
61-65	123 (24.6%)
Age (mean ± SD), years	56.4 ± 4.8
BMI (mean ± SD), kg/m^2	27.8 ± 4.9
Obesity [n (%)]	158 (31.1%)
Diabetes [n (%)]	57 (11.2%)
Systemic arterial hypertension [n (%)]	247 (48.5%)
Dyslipidemia [n (%)]	211 (41.5%)
Smoking [n (%)]	39 (7.7%)
Coronary calcium score (mean ± SD)	21.4 ± 89.7
CIMT (mean ± SD)], mm	0.6 ± 0.1
HR-lowering medication [n (%)]	57 (11.2%)
Exercise testing	
HR response (mean ± SD), bpm	74.4 ± 13.3
Maximum HR (mean ± SD), bpm	152.5 ± 19.6
HR recovery at 1 minute (mean ± SD), bpm	130.7 ± 19.3
Chronotropic index (mean ±SD),%	88.4 ± 20.8
Decreased HR recovery at 1 minute (mean ± SD), bpm	21.8 ±9.1
Functional capacity (mean ± SD), %	104.1 ± 26.9
Exercise time, (mean ±SD), minutes	7.4 ± 2.1
VO_2 (mean ± SD), METs	7.6 ± 2.0
Arrhythmia [n (%)]	43 (9.9%)

BMI: body mass index; CIMT: carotid intima-media thickness; HR: heart rate; METs: metabolic equivalents; SD: standard deviation; VO_2: oxygen uptake

Regarding the percentage of women at high risk based on the FRS (13.6% of the women), after reclassification, it increased to 14.4% with the addition of one-minute HR recovery ≤12 bpm and to 17.1% with the addition of a calcium score >0. The percentage of women at low risk based on the FRS (80.2%) decreased due to the migration of women to the strata of higher risk, from 80.2% to 50.6% when considering a premature family history of a cardiovascular event, and to 77.2% when considering the ST-segment depression.

With the incorporation of the variables used to reclassify cardiovascular risk of asymptomatic middle-aged women (Figure 2), the total increase in risk (low to intermediate and intermediate to high) ranged from 3.0% (ST-segment depression) to 29.7% (premature family history of cardiovascular event). For all variables considered, the highest increment occurred in the intermediate-risk stratum.

Discussion

This study demonstrated that adding the variables premature family history of cardiovascular events, exercise test parameters, and markers of subclinical

Table 2 – Prevalence of premature family history of cardiovascular events, exercise testing variables, and subclinical atherosclerosis markers in asymptomatic middle-aged women according to the Framingham Risk Score classification

Variable	Framingham Risk Score*								p†
	Low		Intermediate		High		Total		
	N	%	N	%	N	%	N	%	
Premature family history of AMI and/or sudden death									
Yes	146	37.0	13	41.9	25	37.9	184	37.4	0.856
Not	249	63.0	18	58.1	41	62.1	308	62.6	
Chronotropic index									
Altered (<62%‡/<80%)	104	25.9	14	45.2	22	32.4	140	28.0	0.049
Normal	297	74.1	17	54.8	46	67.6	360	72.0	
Decreased HR recovery at 1 minute									
Altered (≤12 bpm)	52	12.9	5	16.7	12	17.6	69	13.8	0.520
Normal	350	87.1	25	83.3	56	82.4	431	86.2	
Functional capacity									
Altered (<85%)	90	22.4	8	25.8	20	29.4	118	23.6	0.430
Normal	312	77.6	23	74.2	48	70.6	383	76.4	
ST-segment depression									
Yes	15	3.7	1	3.2	6	8.8	22	4.4	0.157
Not	387	96.3	30	96.8	62	91.2	479	95.6	
Coronary calcium score									
Zero	264	76.5	13	52.0	41	71.9	318	74.5	0.022
1-99	68	19.7	8	32.0	9	15.8	85	19.9	
≥ 100	13	3.8	4	16.0	7	12.3	24	5.6	
CIMT									
≤1 mm	360	89.6	27	87.1	55	80.9	442	88.2	0.120
>1 mm and/or carotid plaque	42	10.4	4	12.9	13	19.1	59	11.8	

AMI: acute myocardial infarction; HR: heart rate; CIMT: carotid intima-media thickness.
**Framingham Risk Score: low (<5%), intermediate (5-10%), high (>10%); †p-value referring to the Pearson chi-square test; ‡Chronotropic index <62% only in women using heart rate-lowering medication.*
Note: Women with incomplete information were excluded from the analyses.

atherosclerosis to the FRS provided a cardiovascular risk reclassification in asymptomatic, middle-aged women. Among the seven variables used, ST-segment depression contributed to the smallest increase (3%) in cardiovascular risk when added to the FRS, while other variables like premature family history of cardiovascular events (about 30%) and altered chronotropic index (about 21%) contributed to the largest increases.

Despite the recognized importance of the FRS, studies[3,27,29] have drawn attention to the use of some variables for reclassification of the cardiovascular risk in middle-aged women, since although most of them are classified as low risk by the FRS, some are affected by acute myocardial infarction, even without previous symptoms. Thus, for women at low or intermediate risk based on the FRS, with one or more risk factors or

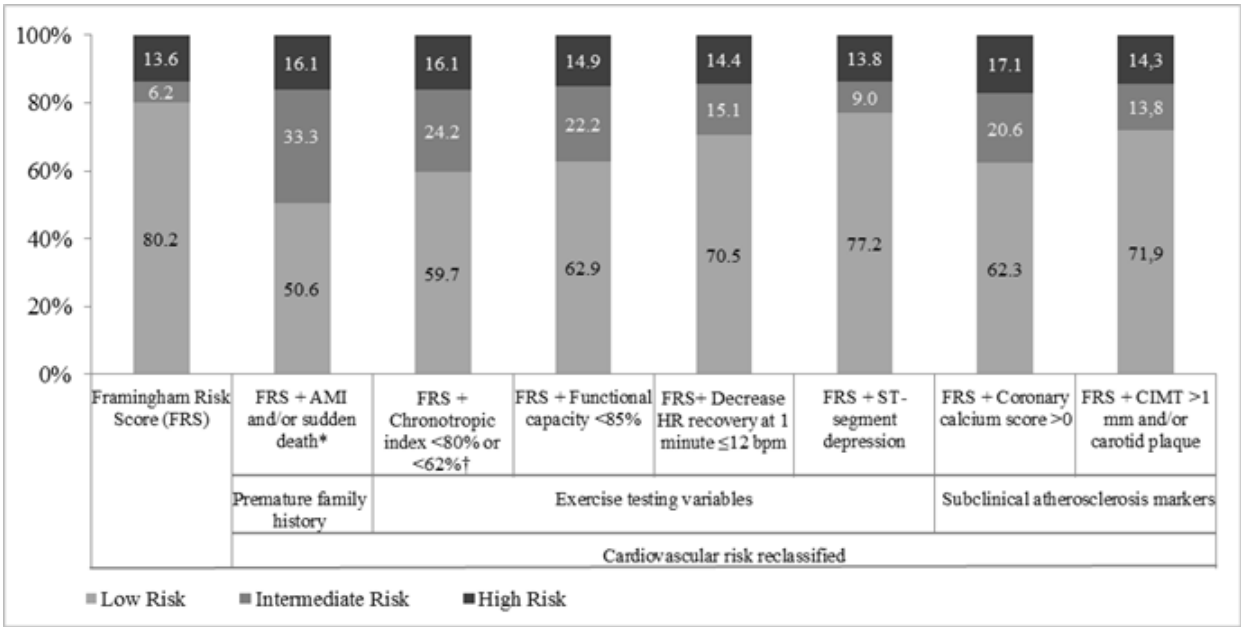


Figure 1 – Proportion of asymptomatic middle-aged women by Framingham Risk Score strata and by risk reclassification after addition of premature family history of cardiovascular event, exercise testing variables, and subclinical atherosclerosis markers
FRS: Framingham Risk Score; AMI: acute myocardial infarction; HR: heart rate; CIMT: carotid intima-media thickness.
**History of acute myocardial infarction (AMI) and/or sudden death in parents and/or siblings younger than 55 years (men) or 60 years (women); †Chronotropic index <62% if using heart rate-lowering medication.*

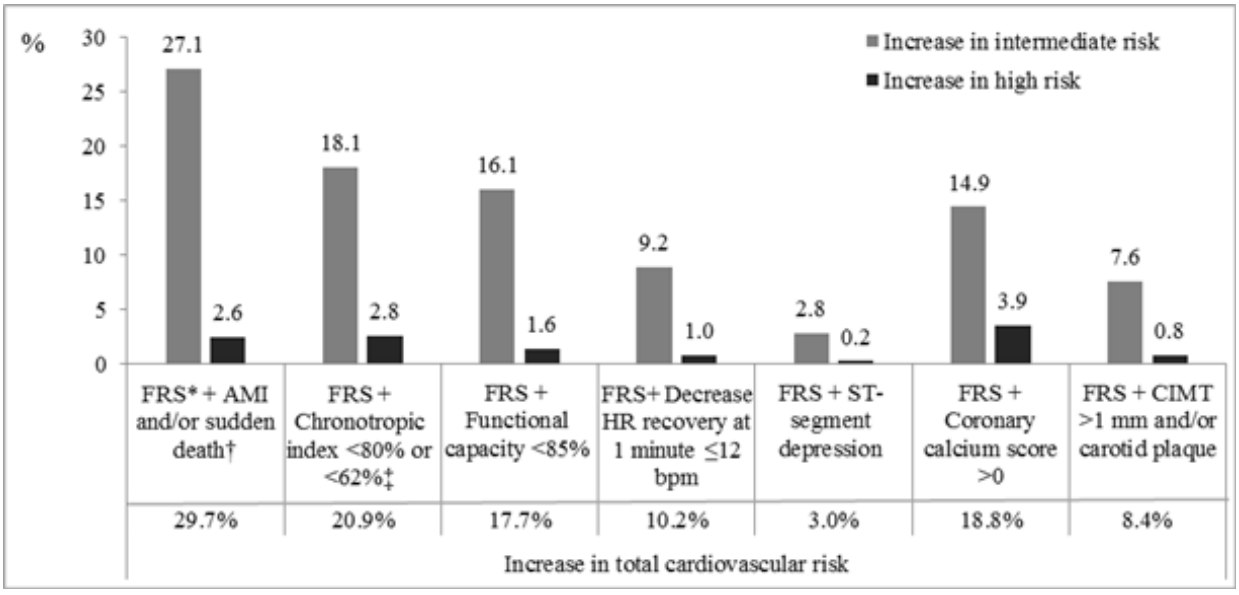


Figure 2 – Increase in cardiovascular risk by the addition of premature family history of cardiovascular events, exercise testing variables, and subclinical atherosclerosis markers to the Framingham Risk Score in asymptomatic middle-aged women
FRS: Framingham Risk Score; AMI: acute myocardial infarction; HR: heart rate; CIMT: carotid intima-media thickness
**FRS: Framingham Risk Score; †History of acute myocardial infarction (AMI) and/or sudden death in parents and/or siblings younger than 55 years (men) or 60 years (women); ‡Chronotropic index <62% if using heart rate-lowering medication*

a positive family history, the addition of other variables to the risk score may identify and benefit those most vulnerable to cardiovascular events.[39]

Several variables have been proposed for reclassification of cardiovascular risk estimated by the FRS,[3,27,29] varying from simple clinical history to more complex methods that are expensive or require advanced technology, such as cardiac imaging tests. The variables analyzed in the present study were previously shown to be associated with severe outcomes, [3,11,16-18,23,26,29] including death, acute myocardial infarction, and stroke. Five of the seven variables showed a homogeneous distribution between the FRS strata, which reinforces the possible benefit of their addition to this traditional risk score.

A premature family history of cardiovascular events in parents and siblings has been independently associated with a higher incidence of cardiovascular events, even in women classified as low risk by the FRS.[1,13,40,41] This is a class I variable in asymptomatic individuals[10] obtained during the initial evaluation, regardless of other exams and at no additional cost.

The predictive factors of mortality, although easily assessed in exercise testing, are not always considered important in the interpretation of the test results, including in asymptomatic women,[26,29,42] and are not considered for primary prevention. As noted in this study, about one-fifth of asymptomatic middle-aged women would be more closely monitored for their cardiovascular risk if abnormalities in the chronotropic index or functional capacity were added to the FRS. A low functional capacity is potentially reversible by physical activity programs aimed to reduce cardiovascular risk.[26,33,34,43,44] On the other hand, a good functional capacity is indicative of better prognosis, even in the presence of ischemia, elevated calcium score, or anatomical coronary disease.[34,45,46] Also, the finding of a good functional capacity, can avoid the overvaluation of eventual ST-segment depression and the subsequent performance of unnecessary or even harmful exams.

In relation to the coronary calcium score and CIMT, studies[3,11,12] have shown that they add independent prognostic information to the FRS. In the present study, the increment in cardiovascular risk by the addition of CIMT >1 mm and/or carotid plaque to the FRS was lower than that observed with the addition of a carotid calcium score >0. However, access to both tests may be costly and not possible in clinical practice. In this case, we consider the CIMT due to the higher feasibility and lack of radiation exposure.

Among the strengths of the study, our study population consisted of middle-aged women whose complaints may go unmonitored and uninvestigated, despite the increase in the prevalence and severity of cardiovascular diseases in this group.[3,4,40] Middle-aged women have relatively low participation rates in clinical trials and scientific guidelines.[47,48] In addition, we analyzed variables that are easily measured by exercise testing but not always valued in clinical practice.[21-23,49] It should be emphasized that exercise testing is a widespread, low-cost method, that does not involve radiation, with proven accuracy in different populations, including asymptomatic women.[20,24,30] In this study, exercise testing was symptom-limited, rather than by maximal HR, which could have underestimated functional capacity.[29,30]

In the present study, we evaluated whether the addition of certain variables to the FRS would improve risk classification in asymptomatic middle-aged women, and propose that premature family history of cardiovascular events should be the first factor to be evaluated by clinicians in women classified at low or intermediate risk based on the FRS. Then, after risk reclassification, these women would undergo exercise testing and carotid artery ultrasound for assessment of markers of subclinical atherosclerosis, including the CIMT, and calcium score testing. In each stage, stricter recommendations for periodic follow-up and primary prevention strategies are recommended to early identify those women at higher risk of cardiovascular events.

This study was limited by its cross-sectional design, and the absence of monitoring the effect of adding family history, exercise testing parameters and subclinical atherosclerosis markers on cardiovascular outcomes of these women over time. However, the selection of variables for risk reclassification was based on cohort studies that evaluated severe outcomes such as death, acute myocardial infarction, and stroke.[3,11,16-18,26,29] It is also worth noting that all variables used in the present study to reclassify cardiovascular risk in asymptomatic middle-aged women are currently recommended in national and international guidelines as factors for consideration in risk assessments.[4,9,10,20]

Conclusions

In asymptomatic middle-aged women, the study revealed an increase of 3.0-29.7% in cardiovascular risk estimated by the FRS with the addition of premature family history of acute myocardial infarction and/or

sudden death, mortality predictive factors assessed by exercise testing, and subclinical atherosclerosis markers. This enabled risk reclassification of women classified as low or intermediate risk based on the FRS, and the possibility for a more effective control and reduction of the risk for cardiovascular events in this group of asymptomatic women.

Acknowledgements

The authors are grateful to the staff of Pernambuco Cardiac Emergency Center (*Pronto Socorro Cardiológico de Pernambuco*) and the Oswaldo Cruz University Hospital Study Center, both linked to the University of Pernambuco (Recife – PE, Brazil), for their collaboration and support in the development of the study.

Author contributions

Conception and design of the research: Coutinho RQ, Montarroyos UR, Barros IML, Guimarães MJB, Costa LOBF, Ferreira MNL, Chalela WA, Pedrosa RP. Acquisition of data: Coutinho RQ, Barros IML, Leão APD, Medeiros AKL, Monteiro MF. Analysis and interpretation of the data: Coutinho RQ, Montarroyos UR, Guimarães MJB, Pedrosa RP. Statistical analysis: Montarroyos UR. Obtaining financing: Barros IML. Writing of the manuscript: Coutinho RQ, Montarroyos UR, Guimarães MJB, Pedrosa RP. Critical revision of the manuscript for intellectual content: Coutinho RQ, Montarroyos UR, Guimarães MJB, Ferreira MNL, Chalela WA, Pedrosa RP.

Potential Conflict of Interest

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

Sources of Funding

The study was partially funded by the *Fundação de Amparo à Ciência e Tecnologia do Estado de Pernambuco* (Brazil) - Facepe (process number: APQ-1386-4.00/08).

Study Association

This article is part of the doctoral thesis submitted by Ricardo Quental Coutinho to the University of Pernambuco.

Ethics approval and consent to participate

This study was approved by the Brazilian National Ethics Committee Registry, CAAE n. 0159.0.106.106-11. The research was conducted according to the principles of the Declaration of Helsinki (2013). Written informed consent was obtained from all participants included in the study, who were assured of adequate symptom control or changes in subclinical atherosclerosis markers, if required.

References

1. Fernandes CE, Pinho-Neto JSL, Gebara OCE, Santos Filho RD, Pinto Neto AM, Pereira Filho AS, et al. I diretriz brasileira sobre prevenção de doenças cardiovasculares em mulheres climatéricas e a influência da terapia de reposição hormonal (TRH) da Sociedade Brasileira de Cardiologia (SBC) e da Associação Brasileira do Climatério (SOBRAC). Arq Bras Cardiol. 2008;91(1 supl 1):1-23.
2. Woodard GA, Brooks MM, Barinas-Mitchell E, Mackey RH, Matthews KA, Sutton-Tyrrell K. Lipids, menopause and early atherosclerosis in swan heart women: menopausal transition and lipids. Menopause. 2011;18(4):376-84.
3. Lakoski SG, Greenland P, Wong ND, Schreiner PJ, Herrington DM, Kronmal RA, et al. Coronary artery calcium scores and risk for cardiovascular events in women classified as "low risk" based on Framingham risk score: The multi-ethnic study of atherosclerosis (MESA). Arch Intern Med. 2007;167(22):2437-42.
4. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB, Gibbons R, et al. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014; 63(25):2935-59.
5. Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women-2011 update. A guideline from the American Heart Association. JACC. 2011;57(12):1404-23.
6. Précoma DB, Oliveira GMM, Simão AF, Dutra OP, Coelho OR, Izar COM, et al. Atualização da diretriz de prevenção cardiovascular da Sociedade Brasileira de Cardiologia - 2019. Arq Bras Cardiol. 2019;113(4):787-891.
7. Fernandes PV, Castro MM, Fuchs A, Machado MCR, Oliveira FD, Silva LB, et al. Valor preditivo do escore de Framingham da identificação de alto risco cardiovascular. Int J Cardiovasc Sci.2015;28(1):4-8.
8. Santos RD, Nasir K. Insights into atherosclerosis from invasive and non-invasive imaging studies: should we treat subclinical atherosclerosis? Atherosclerosis. 2009;205(2):349-56.
9. 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(2Supl.1):1-76.
10. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2010;56(25):e50-103.

11. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. Circulation. 2007;115(4):459-67.

12. Sara L, Szarf G, Tachibana A, Shiozaki AA, Villa AV, Oliveira AC, et al. Sociedade Brasileira de Cardiologia. II diretriz de ressonância magnética e tomografia computadorizada cardiovascular da Sociedade Brasileira de Cardiologia e do Colégio Brasileiro de Radiologia. Arq Bras Cardiol. 2014; 103(6Supl.3):1-86.

13. Michos ED, Vasamreddy CR, Becker DM, Yanek LR, Moy TF, Fishman EK, et al. Women with a low Framingham risk score and a family history of premature coronary heart disease have a high prevalence of subclinical coronary atherosclerosis. Am Heart J. 2005;150(6):1276-81.

14. Azevedo CF, Rochitte CE, Lima JAC. Escore de cálcio e angiotomografia coronariana na estratificação do risco cardiovascular. Arq Bras Cardiol. 2012;98(6):559-68.

15. Greenland P, Bonow RO, Brundage BH, Budoff MJ, Eisenberg MJ, Grundy SM, et al. ACCF/AHA 2007 clinical expert consensus document on coronary artery calcium scoring by computed tomography in global cardiovascular risk assessment and in evaluation of patients with chest pain. J Am Coll Cardiol. 2007;49(3):378-402.

16. Detrano R, Guerci AD, Carr JJ, Bild DE, Burke G, Folsom AR, et al. Coronary calcium as a predictor of coronary events in four racial or ethnic groups. N Engl J Med. 2008;358(13):1336-45.

17. Budoff MJ, Shaw LJ, Liu ST, Weinstein SR, Mosler TP, Tseng PH, et al. Long-term prognosis associated with coronary calcification: observations from a registry of 25,253 patients. J Am Coll Cardiol. 2007;49(18):1860-70.

18. van den Oord SC, Sijbrands EJ, ten Kate GL, van Klaveren D, van Domburg RT, van der Steen AFW, et al. Carotid intima-media thickness for cardiovascular risk assessment: systematic review and meta-analysis. Atherosclerosis. 2013;208(1):1-11.

19. Freire CMV, Alcantara ML, Santos SN, Amaral SI, Veloso O, Porto CLL, et al. Recomendação para a quantificação pelo ultrassom da doença aterosclerótica das artérias carótidas e vertebrais: grupo de trabalho do Departamento de Imagem Cardiovascular da Sociedade Brasileira de Cardiologia - DIC - SBC. Arq Bras Cardiol: Imagem cardiovasc. 2015;28(nº especial):e1-e64.

20. Meneguelo RS, Araújo CGS, Stein R, Mastrocolla LE, Albuquerque PF, Serra SM, et al. III diretriz da Sociedade Brasileira de Cardiologia sobre teste ergométrico. Arq Bras Cardiol. 2010; 95(5 supl 1):1-26.

21. Kligfield P, Lauer MS. Contemporary reviews in cardiovascular medicine exercise electrocardiogram testing beyond the ST segment. Circulation. 2006;114:2070-82.

22. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al on behalf of the American Heart Association Exercise, Cardiac Rehabilitation, and Prevention Committee of the Council on Clinical Cardiology, Council on Nutrition, Physical Activity and Metabolism, Council on Cardiovascular and Stroke Nursing, and Council on Epidemiology and Prevention). Exercise standards for testing and training: a scientific statement from the American Heart Association. Circulation. 2013;128:873-934.

23. Kohli P, Gulati M. Exercise stress testing in women: going back to the basics. Circulation. 2010;122(24):2570-80.

24. Mieres JH, Gulati M, Bairey Merz N, Berman DS, Gerber TC, Hayes SN, et al (on behalf of the American Heart Association Cardiac Imaging Committee of the Council on Clinical Cardiology; Cardiovascular Imaging and Intervention Committee of the Council on Cardiovascular Radiology and Intervention). Role of noninvasive testing in the clinical evaluation of women with suspected ischemic heart disease: a consensus statement from the American Heart Association. Circulation. 2014;130(4):350-79.

25. Frolkis JP, Pothier CE, Blackstone EH, Lauer MS. Frequent ventricular ectopy after exercise as a predictor of death. N Engl J Med. 2003;348(9):781-90.

26. Gulati M, Pandey DK, Arnsdorf MF, Lauderdale DS, Thisted RA, Wicklund RH, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. Circulation. 2003;108(13):1554-9.

27. Gupta S, Rohatgi A, Ayers CR, Willis BL, Haskell WL, Khera A, et al. Exercise physiology cardiorespiratory fitness and classification of risk of cardiovascular disease mortality. Circulation. 2011;123:1377-83.

28. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women a meta-analysis. JAMA. 2009;301(19):2024-35.

29. Mora S, Redberg RF, Cui Y, Whiteman MK, Flaws JA, Sharrett AR, Blumenthal RS. Ability of exercise testing to predict cardiovascular and all-cause death in asymptomatic women: a 20-year follow-up of the lipid research clinics prevalence study. JAMA. 2003;290(12):1600-7.

30. Balady GJ, Larson MG, Vasan RS, Leip EP, O'Donnell CJ, Levy D. Usefulness of exercise testing in the prediction of coronary disease risk among asymptomatic persons as a function of the Framingham risk score. Circulation. 2004;110(14):1920-5.

31. Cournot M, Taraszkiewick D, Cambou JP, Galinier M, Boccalon H, Hanaire-Broutin H, et al. Additional prognostic value of physical examination, exercise testing, and arterial ultrasonography for coronary risk assessement in primary prevention. Am Heart J. 2009;158(5):845-51.

32. Chang SM, Nabi F, Xu J, Pratt CM, Mahmarian AC, Frias ME, et al. Value of CACS compared with ett and myocardial perfusion imaging for predicting long-term cardiac outcome in asymptomatic and symptomatic patients at low risk for coronary disease clinical implications in a multimodality imaging world. J Am Coll Cardiol Img. 2015;8(2):134-44.

33. DeFina L, Radford N, Leonard D, Gibbons L, Khera A. Cardiorespiratory fitness and coronary artery calcification in women. Atherosclerosis. 2014;233(2):648-53.

34. Choi SY, Sung J, Park HE, Han D, Chang HJ. Combined effects of exercise capacity and coronary atherosclerotic burden on all-cause mortality in asymptomatic Koreans. Atherosclerosis. 2016;251:396-403.

35. Scheaffer RL, Mendenhall W, Ott RL, Gerow KG. Elementary Survey Sampling. 7th edn. Massachusetts, USA: Cengage Learning, 2011:480p.

36. Bruce RA, Kusumi F, Hosmer D. Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease. American Heart Journal. 1973;85(4):546-51.

37. Karvonen MJ, Kentala E, Mustala O. The effects of training on heart rate; a longitudinal study. Ann Med Exp Biol Fenn. 1957;35(3):307-15.

38. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. J Am Coll Cardiol. 1990;15(4):827-32.

39. Gomes BFO, Oliveira GMM. What is the best cardiovascular risk score for the Brazilian population? Int J Cardiovasc Sci. 2020;33(6):627-28.

40. Benjamin EJ, Blaha MJ, Chiuve SE, Cushman M, Das SR, Deo R, et al. Heart Disease and Stroke Statistics- 2017 Update: A Report From the American Heart Association. Circulation. 2017;135(10):e146-e603.

41. Suh B, Shin DW, Lee SP, Lee H, Lee H, Park E-A, et al. Family history of coronary heart disease is more strongly associated with coronary than with carotid atherosclerosis in healthy asymptomatic adults. Atherosclerosis. 2014;233(2):584-9.

42. Coutinho RQ, Montarroyos UR, Barros IML, Guimarães MJB, Costa LOBF, Medeiros AKL, et al. Non Electrocardiographic alterations in exercise testing in asymptomatic women. Associations with cardiovascular risk factors. Clinics. 2019;74:e1005.

43. Arnson Y, Rozanski A, Gransar H, Hayes SW, Friedman JD, Thomson LEJ, et al. Impact of Exercise on the relationship between CAC scores and all-cause mortality. JACC Cardiovasc Imaging. 2017;10(12):146-68.

44. Blaha MJ, Feldman DI , Nasir K. Coronary artery calcium and physical fitness – the two best predictors of long-term survival. Atherosclerosis. 2014;234(1):93-4.

45. Bourque JM, Holland BH, Watson DD, Beller GA. Achieving an exercise workload of > or = 10 metabolic equivalents predicts a very low risk of inducible ischemia: does myocardial perfusion imaging have a role? J Am Coll Cardiol. 2009;54(6):538-45.

46. Vivekananthan DP, Blackstone EH, Pothier CE, Lauer MS. Heart rate recovery after exercise is a predictor of mortality, independent of the angiographic severity of coronary disease. J Am Coll Cardiol. 2003;42(5):831-8.

47. Kim ES, Menon V. Status of women in cardiovascular clinical trials. Arterioscler Thromb Vasc Biol. 2009;29(3):279-83.

48. Melloni C, Berger JS, Wang TY, Gunes F, Stebbins A, Pieper KS, et al. Representation of Women in Randomized Clinical Trials of Cardiovascular Disease Prevention. Circ Cardiovasc Qual Outcomes. 2010;3(2):135-42.

49. Santos MON, Mees AV, Moraes Júnior A, Santos LR, Leão MO, Rafael PF, et al. Avaliação crítica sobre acurácia do teste ergométrico na prática clínica: experiência de centro único. Rev Bras Cardiol. 2012;25(3):177-184.

ORIGINAL ARTICLE

Cardiovascular Risk Factors, Functionality, and Quality of Life in Climacteric Women

João Vítor Costa dos Santos Chaves,[1] Keila Lindineia Silva Pinto,[1] Kleicillainy Mota de Sousa,[1] Lucas Oliveira Soares,[1] André Luiz Lisboa Cordeiro[1,2]

Centro Universitário Nobre,[1] Feira de Santana, BA - Brazil
Escola Bahiana de Medicina e Saúde Pública, Salvador,[2] BA - Brazil

Abstract

Background: Cardiovascular disease (CVD) comprises a group of cardiac and circulatory diseases. Despite the high incidence in males, women after menopause have an exponential increase in the risk of CVD.

Objective: To identify the leading risk factors for CVD and describe quality of life and functionality in women hospitalized for cardiac causes during the climacteric period.

Materials and methods: Observational descriptive study. Quality of life was assessed through the SF-36 questionnaire, and functionality through the Functional Independence Measurement (FIM) scale. Records were used to identify the main risk factors associated with CVD in climacteric women.

Results: We included 30 patients (mean age, 55 ± 6 years). The mean FIM score was 118 ± 3, and the mean SF-36 score, 20 ± 10. Hypertension and sedentary lifestyle were the most prevalent cardiovascular risk factors in these women.

Conclusion: Hypertension and sedentary lifestyle were the most prevalent cardiovascular risk factors in this sample of climacteric women hospitalized for cardiac causes. Quality of life was strongly affected, with social, emotional, and mental health domains showing the most impact.

Keywords: Climacteric; Quality of life; Cardiovascular disease.

Introduction

Cardiovascular disease (CVD) is a major global public health problem[1] and the leading cause of death in developed countries. Risk factors for CVD can be divided into modifiable and non-modifiable. The modifiable ones include dyslipidemia, smoking, hypertension, diabetes mellitus, physical inactivity, and obesity. The non-modifiable ones are age, sex, and family history.[2]

Among the most prevalent cardiovascular diseases in this population, patients with CVD, are heart failure (HF) and coronary artery disease (CAD).[3-6]

The climacteric is defined as a biological phase of life, not a pathological process, which comprises the changes that occur between the reproductive and non-reproductive periods of a woman's life. This stage of the life cycle, which can be divided into premenopausal, peri-menopausal, and postmenopausal phases, predisposes women to a set of signs and symptoms known as the climacteric syndrome. It is also a risk factor for several conditions, including CVD.[7] This increased risk is related to hormonal, circulatory and blood changes that occur during the climacteric.[8,9]

CVD and its risk factors have a negative impact on quality of life. Reductions in peripheral muscle endurance during hospitalization has a negative impact on functionality, resulting in increased care costs and reduced quality of life. It is essential to avoid and mitigate loss of muscle conditioning

Keila Lindineia Silva Pinto
Physiotherapist
Graduated from Centro Universitário Nobre, Feira de Santana - Bahia

Mailing Address: André Luiz Lisboa Cordeiro
Avenida Dom João VI, 275. Postal Code: 40050-420, Salvador, BA – Brazil.
E-mail: andrelisboacordeiro@gmail.com

DOI: https://doi.org/10.36660/ijcs.20200410

Manuscript received December 19, 2020; revised manuscript March 28, 2021; accepted May 27, 2021.

as early as possible in hospitalized patients, as immobilization or reduced weight support due to hospitalization can result in neuromuscular, cardiovascular, respiratory, and cognitive complications, impacting quality of life and persisting for up to five years after hospital discharge.[8]

The aim of this study was to identify the main risk factors for CVD and to describe quality of life and functionality level in women hospitalized during the climacteric period.

Materials and Methods

This was an observational descriptive study conducted at a cardiology referral hospital in the state of Bahia, Brazil. The study was approved by the Research Ethics Committee of *Faculdade Nobre* with opinion number 2.002.947. All participants provided written informed consent.

Eligibility Criteria

The inclusion criteria were female sex, age >45 years, and hospitalization for cardiac causes (such as acute myocardial infarction, heart failure, or cardiac surgery). The exclusion criteria were any factors that precluded completion of the questionnaires, such as neurological disorders, mental confusion, and preexisting cognitive limitations, as well as refusal to provide informed consent. Participants were recruited by convenience, with no sample size calculation.

Study Protocol

Patients who met the inclusion criteria and agree to participate were evaluated during hospitalization. The Medical Outcomes Study 36 - Item Short-Form Health Survey (SF-36) questionnaire was administered to assess quality of life, and the Functional Independence Measurement (FIM) scale, to assess functionality. In addition, we identified the main risk factors for CVD, such as hypertension, diabetes mellitus, and dyslipidemia, through a review of medical records. Participants were considered physically inactive if they engaged in less than 150 min/week of physical activity, as assessed by the International Physical Activity Questionnaire (IPAQ). Patients were further categorized as nonsmokers or smokers (current or former). Those with a smoking cessation period longer than one year were considered former smokers.

Measurement Instruments

The FIM assesses the individual's degree of performance on a set of 18 basic and instrumental tasks of daily living, involving self-care, sphincter control, transfers, locomotion, communication, and social cognition. The scale includes motor (FIMm), cognitive (FIMc), and total (FIMt) domains. Its total score ranges from 18 to 126; each item can be rated from 1 to 7, with a value of 1 corresponding to total dependence and a value of 7 corresponding to normal performance of tasks in an independent manner.[10]

To assess the quality of life of the patients, the SF-36 questionnaire was applied. Numerous instruments can be used for quality-of-life studies. The SF-36 is a generic, easily administered, and understandable quality of life assessment tool.[11]

The SF-36 consists of 36 items across 8 scales: physical functioning (10 items), role limitations due to physical aspects (4 items), bodily pain (2 items), general health (5 items), energy/fatigue (4 items), social functioning (2 items), role limitations due to emotional aspects (3 items), and emotional well-being (5 items), which assess both negative aspects of health (illness or disease) as well as positive aspects (well-being). The questionnaire was designed to study the quality of life of people with more than one condition or to reflect the impact of a disease on patients' lives in diverse populations, and to narrowly assess certain aspects of quality of life. The questionnaire has a final score of zero to 100 points, where zero corresponds to the worst and 100 to the best perception of quality of life.

Statistical Analysis

A descriptive analysis of the data was performed in SPSS 20.0. Data were expressed as means and standard deviations or absolute and relative frequencies, as appropriate.

Results

During the study period, 30 climacteric women, all admitted to the study hospital for cardiac causes, were enrolled in the sample. The mean age was 55 ± 6 years, and the mean body mass index was 23 ± 3 kg/m^2. Table 1 shows the reasons for admission and CVD risk factors of the participants.

Table 2 presents the participants' functional independence and quality of life, as assessed by the FIM and SF-36. The mean FIM score was 118 ± 3. The highest mean SF-36 scores were found in the physical functioning domain (75 ± 5), while the lowest occurred in the bodily pain domain (20 ± 10).

Table 1 – Clinical data of study participants

Variable	Total patients (n = 30)
Age (years)	55 ± 6
Body mass index (kg/m²)	23 ± 3
Reason for admission	
Cardiac surgery	15 (50%)
Acute myocardial infarction	9 (30%)
Heart failure	6 (20%)
Cardiovascular risk factors	
Diabetes mellitus	13 (43%)
Hypertension	18 (60%)
Dyslipidemia	15 (50%)
Sedentary lifestyle	17 (57%)
Smoking	6 (20%)
Length of stay (days)	5 ± 2

Table 2 – Functional independence and quality of life of participants

Variable	Mean ± standard deviation
Functional Independence Measure	**118 ± 3**
Quality of life	
Physical functioning	75 ± 5
Role limitations, physical	70 ± 8
Bodily pain	20 ± 10
General health	70 ± 5
Energy/fatigue	60 ± 10
Social functioning	30 ± 5
Role limitations, emotional	40 ± 10
Emotional well-being	50 ± 12

Discussion

The present study found that, in a convenience sample of climacteric women admitted to a cardiology referral hospital, hypertension and physical inactivity were the most prevalent risk factors for CVD.

Studies have shown that the prevalence of hypertension increases gradually with age; in women, this process occurs especially in the early postmenopausal phase.[12] Some studies suggest that regular (daily) physical activity has a positive effect on the endothelium and may attenuate vasodilation, preserving nitric oxide bioavailability and resulting in healthier natural aging for women.[13] In our sample, physical inactivity was highly prevalent.

A key component of reducing modifiable risk factors for CVD is to raise awareness of their potential for harm. Nevertheless, most patients interviewed noted that they were already aware of the risk factors, but did not engage in physical activity or weight loss to reduce these factors. Pursuing healthier lifestyles, engaging in physical activity, smoking cessation, periodic control of blood pressure, and nutritional counseling are appropriate for proper weight maintenance and control og blood glucose and cholesterol.

Half of the women surveyed had some type of dyslipidemia. This finding reinforces the importance of identifying and treating dyslipidemia during the climacteric in order to reduce morbidity and mortality rates in women.[14]

Compared to other studies, smoking was the most frequently identified risk factor (one in two women evaluated). This result is consistent with that found by other studies within Brazil, but with a lower prevalence than those reported.[15] Concern about smoking is explained by the fact that nicotine, by autonomic stimulation, promotes acceleration of heart rate and spasm of arterial vessels, contributing to hypertension.

During the climacteric, women go through a process of gradual physiological transition due to decreased estrogen, resulting in postmenopausal changes.[16] In addition to the typical disorders of this period, women undergo other physiological changes that may begin to emerge around age 40 and extend to age 70 in rarer cases. Physical and/or emotional disorders may arise in certain stages of the climacteric—feelings of failure, aging, mood swings, and beauty—and affect quality of life.[17-20]

One study reports that 50% to 70% of climacteric women manifest somatic symptoms and emotional difficulties. In addition, preexisting clinical comorbidities, may explain many of these somatic

and emotional complaints.[21] Another study showed that when women were asked about comorbidities, there was a significant prevalence of self-reported hypertension—about 30% distributed across groups.[22] This corroborates the predominance of hypertension in the present study.

Variations in steroid hormones and opioid peptides during the climacteric period seem to interfere with regulation of the hypothalamic thermoregulatory system; this dysfunction, in turn, may favor onset of the vasomotor symptoms of menopause. Therefore, the more severe this dysfunction, the worse the woman's quality of life and possibility of developing depressive episodes.[23] It is therefore understandable why the participants of the present study scored poorly on the emotional domains of the SF-36, with values considered low when compared to the non-climacteric period.

The presence of any chronic disease was related to a deterioration in quality of life in the emotional well-being and general health domains. It is believed that the onset of illness directly affects quality of life, and the higher the number of chronic diseases, the worse the quality of life.[24] According to the SF-36, physical functioning reached an average score of 75 of the interviewed patients, which indicates these women did not experience a decrease in functional capacity during the climacteric. However, they reported a significant increase in bodily pain this period.

Given these risk factors, it is of great importance to develop programs and strategies aimed at health promotion, symptom relief, prevention, and control of the most frequent cardiovascular diseases, seeking to improve the quality of life of this population.

Among the limitations of the study, we can highlight the lack of sample size calculation and the absence of follow-up monitoring to verify patients' outcomes.

Conclusion

Hypertension and sedentary lifestyle were the most prevalent cardiovascular risk factors in this sample. Quality of life was significantly affected, with social, emotional, and mental health domains showing the most impact.

Author contributions

Conception and design of the research: Chaves JVCS, Cordeiro ALL, Pinto KLS, Sousa KM. Acquisition of data: Chaves JVCS, Pinto KLS, Sousa KM. Analysis and interpretation of the data: Chaves JVCS, Cordeiro ALL. Statistical analysis: Cordeiro ALL. Writing of the manuscript: Cordeiro ALL, Pinto KLS, Sousa KM. Critical revision of the manuscript for intellectual content: Oliveira L.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Faculdade Nobre* under the protocol number 2.002.947. 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. Costa FAZ, Parente FL, Farias MS, Parente FL, Francelino PC, Bezerra LTL. Perfil demográfico de pacientes com infarto agudo do miocárdio no brasil: revisão integrativa. San Rev Polit Publ. 2018;17(2):66-73. doi: 10.36925/sanare.v17i2.1263.

2. Melo JB, Campos RCA, Carvalho PC, Meireles MF, Andrade MVG, Rocha TPO. Cardiovascular risk factors in climacteric women with coronary artery disease. Int J Cardiovasc Sci. 2018;31(1):4-11. doi: 10.5935/2359-4802.20170056.

3. World Health Organization. Cardiovascular diseases (CVDs) [Internet]. Geneva: WHO; 2017 [cited 2021 Jun 8]. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)

4. Sousa MM, Oliveira JDS, Soares MJGO, Bezerra SMMDS, Araújo AA, Oliveira SHDS. Association of social and clinical conditions to the quality of life of patients with heart failure. Rev Gaucha Enferm. 2017;38(2):e65885. Portuguese, English. doi: 10.1590/1983-1447.2017.02.65885.

5. Vargas RA, Riegel F, Oliveira N Jr, Siqueira DS, Crossetti MGO. Qualidade de vida de pacientes pós-infarto do miocárdio: revisão integrativa da literatura. Rev Enferm Ufpe Online. 2017;11(7); 2803-09. doi: 10.5205/reuol.10939-97553-1-RV.1107201721.

6. Silveira EL, Cunha LM, Pantoja MS, Lima AVM, Cunha ANA. Prevalência e distribuição de fatores de risco cardiovascular em portadores de doença

arterial coronariana no Norte do Brasil. Rev Fac Cienc Med de Sorocaba. 2018;20(3):167-173. doi: 10.23925/1984-4840.2018v20i3a9.

7. Texeira VC, Magalhães EP, Araújo DCR, Carneiro JA, Costa FM. Obesidade no climatério: fator de risco para o desenvolvimento de doenças cardiovasculares. Renome. 2015;4(2):29-36.

8. Paciuc J. Hormone therapy in menopause. Adv Exp Med Biol. 2020;1242:89-120. doi: 10.1007/978-3-030-38474-6_6.

9. Anagnostis P, Paschou SA, Katsiki N, Krikidis D, Lambrinoudaki I, Goulis DG. Menopausal Hormone therapy and cardiovascular risk: where are we now? Curr Vasc Pharmacol. 2019;17(6):564-572. doi: 10.2174/1570161116666180709095348.

10. Riberto M, Miyazaki MH, Jucá SSH, Sakamoto H, Pinto PPN, Battistela LR. Validação da versão brasileira da medida de independência funcional. Acta Fisiatr. 2004;11(2):72-6. doi: 10.5935/0104-7795.20040003.

11. Ciconelli RM. Tradução para o português e validação do questionário genético de avaliação de qualidade de vida "Medical Outcomes Study 36"- Item Short-Form Health Survey (SF-36) [dissertation]. São Paulo: Universidade Federal de São Paulo; 1997.

12. Fernandes CE, Pinho-Neto JSL, Gebara OCE, Santos Filho RD, Pinto Neto AM, Pereira Filho AS, et al. I Diretriz brasileira sobre prevenção de doenças cardiovasculares em mulheres climatéricas e a influência da terapia de reposição hormonal (TRH) da Sociedade Brasileira de Cardiologia (SBC) e da Associação Brasileira do Climatério (SOBRAC). Arq Bras Cardiol.2008;91(1 suppl 1):1-23.

13. Di Blasio A, Ripari P, Bucci I, Di Donato F, Izzicupo P, D'Angelo E, et al. Walking training in postmenopause: effects on both spontaneous physical activity and training-induced body adaptations. Menopause. 2012;19(1):23-32. doi: 10.1097/gme.0b013e318223e6b3.

14. Souza LJ, Souto Filho JT, Souza TF, Reis AF, Gicovate Neto C, Bastos DA, et al. Prevalence of dyslipidemia and risk factors in Campos dos Goytacazes, in the Brazilian state of Rio de Janeiro. Arq Bras Cardiol. 2003;81(3):249-64. doi: 10.1590/s0066-782x2003001100005.

15. Borges TT, Rombaldi AJ, Knuth AG, Hallal PC. Knowledge on risk factors for chronic diseases: a population-based study. Cad Saude Publica. 2009;25(7):1511-20. Portuguese. doi: 10.1590/s0102-311x2009000700009.

16. Van der Leeuw J, Wassink AM, Van der Graaf Y, Westerveld HE, Visseren FL. Second Manifestations of ARTerial Disease (SMART) Study Group. Age-related differences in abdominal fat distribution in premenopausal and postmenopausal women with cardiovascular disease. Menopause.2013;20(4):409-17.

17. Hoffmann M, Mendes KG, Canuto R, Garcez Ada S, Theodoro H, Rodrigues AD, Olinto MT. Padrões alimentares de mulheres no climatério em atendimento ambulatorial no Sul do Brasil [Dietary patterns in menopausal women receiving outpatient care in Southern Brazil]. Cien Saude Colet. 2015;20(5):1565-74. Portuguese. doi: 10.1590/1413-81232015205.07942014.

18. Bień A, Rzońca E, Iwanowicz-Palus G, Pańczyk-Szeptuch M. The influence of climacteric symptoms on women's lives and activities. Int J Environ Res Public Health. 2015;12(4):3835-46. doi: 10.3390/ijerph120403835.

19. Larroy C, Quiroga-Garza A, González-Castro PJ, Robles Sánchez JI. Symptomatology and quality of life between two populations of climacteric women. Arch Womens Ment Health. 2020;23(4):517-25. doi: 10.1007/s00737-019-01005-y.

20. Santos RSD, Andrade MM, Ribeiro KMOBF, Nascimento RAD, Vieira MCA, Câmara SMAD, et al. Relationship between vestibular dysfunction and quality of life in climacteric women. Cien Saude Colet. 2020;25(2):645-54. doi: 10.1590/1413-81232020252.00972018.

21. De Lorenzi DR, Baracat EC, Saciloto B, Padilha I Jr. Fatores associados à qualidade de vida após menopausa [Factors related to quality of life in post-menopause]. Rev Assoc Med Bras. 2006;52(5):312-7. doi: 10.1590/s0104-42302006000500017.

22. Silva MNM, Brito LMO, Chein MBC, Brito LGO, Navarro PAAS. Depressão em mulheres climatéricas: análise de mulheres atendidas ambulatoriamente em um hospital universitário no Maranhão. Rev Psiquiatr Rio Gd Sul. 2008;30(2):150-54. doi: 10.1590/S0101-81082008000300011.

23. Miranda JS, Ferreira Mde L, Corrente JE. Quality of life of postmenopausal women attended at Primary Health Care. Rev Bras Enferm. 2014;67(5):803-9. Portuguese. doi: 10.1590/0034-7167.2014670519.

24. Serpa MA, Lima AA, Guimarães ACP, Carrilo MRGG, Coura-Vital W, Veloso VM. Fatores associados à qualidade de vida em mulheres no climatério. Reprod Clim. 2016;31(2)76-8. doi: 10.1016/j.recli.2016.04.001.

Int J Cardiovasc Sci. 2021; 34(4):398-399

EDITORIAL

Climacteric Period and Cardiovascular risk: a Golden Opportunity to Watch and Succeed!

Catarina Sousa[1]

Centro Cardiovascular da Universidade de Lisboa (CCUL), Centro Académico de Medicina de Lisboa (CAML), Faculdade de Medicina da Universidade de Lisboa[1], Lisboa – Portugal

Editorial referring to the article: Cardiovascular Risk Factors, Functionality, and Quality of Life in Climacteric Women

The gradual loss of ovarian function with concomitant decrease in estrogen levels, characteristic of the climacteric period, leads to several metabolic changes and symptoms. Significant effects on the health and quality of life of women occur, and vasomotor symptoms during this transitional period are almost universally recognized. Among physical symptoms, hot flushes and night sweats are very prevalent and may be very disturbing.

However, cardiovascular risk is frequently neglected not only by these women, but surprisingly, also by part of the medical community.[1] Metabolic changes of the climaterium are associated with increased risk of diabetes mellitus, metabolic syndrome and cardiovascular disease.[2] Additionally, the rate of cardiovascular events markedly increases after the age of 45. This is extremely relevant, as cardiovascular disease is the single most frequent cause of death among women.[3]

Scientific societies have played a crucial role in promoting initiatives to increase awareness and to reduce gender disparities regarding cardiovascular outcomes.[4] Multidisciplinary action is required. Primary care physicians, cardiologists and gynecologists should all be actively involved in the care of women, particularly during the climacteric period. Collaboration is essential to allow for early identification of cardiovascular risk factors that are amenable to interventions.

A consensus statement published in 2007 by European cardiologists and gynecologists[2] summarized the available evidence at the time regarding cardiovascular risk among peri-menopausal women. The document aimed at increasing global awareness and setting specific goals to reduce the burden of cardiovascular diseases and improve overall management of this population. Still, more than a decade later, cardiovascular diseases are still a major cause of mortality and loss of quality of life in these women. Additionally, patients' acknowledgement of the disease risk and its impact on their lives has received more and more attention in the last decades.[5] Patient reported outcome measures (PROM) have emerged as important outcomes in disease impact, specifically in the cardiovascular field and may be particularly in climacteric women.

In this issue of the IJCS, a study by Chaves et al.[6] presents a descriptive analysis of a cohort of 30 women over 45 years old hospitalized with cardiovascular disease, namely heart failure, acute coronary syndrome or indication for cardiac surgery. Besides the traditional characterization of demographic data and cardiovascular risk factors of this population, the authors applied two scores – the Functional Independence Measurement (FIM) and the Medical Outcome Study Questionnaire Short Form 36 (SF 36). FIM was initially used in rehabilitation hospitalized patients and has been applied as a generic score to evaluate functional performance.[7] SF 36[8] assesses the health status of patients and includes eight items: 1) limitations in physical activities due to health problems; 2) limitations in social activities due to physical or emotional problems; 3) role limitations due to emotional problems; 4) bodily pain; 5) general mental health (psychological distress and well-being); 6) role limitations due to emotional problems; 7) vitality (energy and fatigue); and 8) general health perceptions. Arterial hypertension, dyslipidemia and sedentary lifestyle were highly prevalent and affected at least half of the patients. This group had a good perception of their functional and physical capacity. On the other

Keywords

Climacteric Period; Cardiovascular Risk; Quality of Life.

Mailing Address: Catarina Sousa
Centro Cardiovascular Universidade Lisboa - Faculdade de Medicina de Lisboa
Av. Prof. Egas Moniz MB. Postal Code: 1648-028, Lisboa – Portugal
E-mail: catarinasousacardio@gmail.com

DOI: https://doi.org/10.36660/ijcs.20210159

Catarina de Sousa, MD
Cardiologist
Invited assistant of Cardiology at Faculty of Medicine - University of Lisbon (FMUL)
Researcher at the Cardiovascular Center of the University of Lisbon (CCUL)

hand, perception of social and emotional aspects as well as mental health were diminished.

In fact, a high prevalence of cardiovascular risk factors in this group is not surprising. Other studies have reported similar findings.[9,10] Blood pressure increases with age due to vascular stiffening. A decrease in vasorelaxation is observed with the decline in estrogen levels in the post-menopause, in addition to an increase in plasma renin activity. Sympathetic overactivity and insulin resistance also occur, which further contributes to increasing blood pressure and the emergence of metabolic disorders.

Interestingly, despite the perception of preserved functional and physical capacity, these women report a low level of regular physical activity. Additionally, a low sense of social, emotional, and mental status was noted. During the climacteric period, weight gain and change in fat distribution are frequent. Furthermore, vasomotor symptoms are also more frequent in women who are physically less active.[11] Thus, in this particular period, regular physical exercise can play a favourable effect on body composition, body weight and bone mineral density, counteracting the overall metabolic changes, with a positive effect on the control of cardiovascular risk factors. It is also crucial in the control of somatic symptoms (probably overvalued by women when compared to the awareness of identifying and controlling cardiovascular risk factors) and improvement in the quality of life and sense of well-being.

We might say that the sample was too small for further associations. The authors could have gone further in the analysis of other cardiovascular risk factors and associations with other important physical variables, such as waist circumference, heart rate, and blood pressure. A more detailed description of the clinical condition affecting the patient was also warranted. "Cardiac surgery" is a very vague term, and the lack of clinical follow-up, acknowledged by the authors, limits the conclusions and applicability of this study, as no inferential analysis was performed.

Nevertheless, this group represents the real-world population of climacteric women, with a high prevalence of cardiovascular risk factors and cardiac diseases.

In summary, this "natural" transitional phase in women carries a high burden of cardiovascular risk and diminished quality of life. Multidisciplinary programs are needed to assist women during this transitional phase, in terms of symptom control, management of cardiovascular risk factors and emotional status, improving the quality of life and ultimately their lifetime prognosis.

References

1. Merz CNB, Andersen H, Sprague E, Burns A, Keida M, Walsh MN, et al. Knowledge, Attitudes, and Beliefs Regarding Cardiovascular Disease in Women: The Women's Heart Alliance. J Am Coll Cardiol. 2017;70(2):123-32. doi: 10.1016/j.jacc.2017.05.024.
2. Collins P, Rosano G, Casey C, Daly C, Gambacciani M, Hadji P, et al. Management of Cardiovascular Risk in the Peri-Menopausal Woman: A Consensus Statement of European Cardiologists and Gynaecologists. Eur Heart J. 2007;28(16):2028-40. doi: 10.1093/eurheartj/ehm296.
3. Global Burden of Disease Study 2019 (GBD 2019) results. Global Health Data Exchange website [Internet]. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2019 [cited 2021 Jun 18]. Available from: http:// ghdx.healthdata.org/gbd-results-tool.
4. Mosca L, Barrett-Connor E, Wenger NK. Sex/Gender Differences in Cardiovascular Disease Prevention: What a Difference a Decade Makes. Circulation. 2011;124(19):2145-54. doi: 10.1161/CIRCULATIONAHA.110.968792.
5. Algurén B, Coenen M, Malm D, Fridlund B, Mårtensson J, Årestedt K, et al. A Scoping Review and Mapping Exercise Comparing the Content of Patient-Reported Outcome Measures (PROMs) Across Heart Disease-Specific Scales. J Patient Rep Outcomes. 2020;4(1):7. doi: 10.1186/s41687-019-0165-7.
6. Chaves JVCS, Pinto KLS, Sousa KM, Soares LO CA. Cardiovascular risk factors, functionality and quality of life of women in climacteric period. Int J Cardiovasc Sci. 2021; 34(4):393-397. doi: https://doi.org/10.36660/ijcs.20200410.
7. Dodds TA, Martin DP, Stolov WC, Deyo RA. A Validation of the Functional Independence Measurement and its Performance Among Rehabilitation Inpatients. Arch Phys Med Rehabil. 1993;74(5):531-6. doi: 10.1016/0003-9993(93)90119-u.
8. Ware JE Jr, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36). I. Conceptual Framework and Item Selection. Med Care. 1992;30(6):473-83.
9. Melo JB, Campos RCA, Carvalho PC, Meireles MF, Andrade MVG, Rocha TPO, et al. Cardiovascular Risk Factors in Climacteric Women with Coronary Artery Disease. Int J Cardiovasc Sci. 2018;31(1):4-11. doi: 10.5935/2359-4802.20170056.
10. Mota MPS, Moura ICG, Marinho RM, Sternick EB, Almeida AM. Evaluation of Cardiovascular Risk in Climacteric Women: A Cross-Sectional Study. J Midlife Health. 2018;9(3):123-29. doi: 10.4103/jmh.JMH_67_18.
11. Gold EB, Sternfeld B, Kelsey JL, Brown C, Mouton C, Reame N, et al. Relation of Demographic and Lifestyle Factors to Symptoms in a Multi-Racial/Ethnic Population of Women 40-55 Years of Age. Am J Epidemiol. 2000;152(5):463-73. doi: 10.1093/aje/152.5.463.

Int J Cardiovasc Sci. 2021; 34(4):400-408

ORIGINAL ARTICLE

Clinical Characteristics and Therapeutic Adherence of Women in a Referral Outpatient Clinic for Severe Hypertension

Pedro Henrique Barletta,[1] Eduardo Faria Soares de Magalhães,[1] Vitor Fernandes de Almeida,[1] Júlia Lasserre Moreira,[1] Murilo Jorge da Silva,[1] Cristiano Macedo,[2] Roque Aras[1]

Faculdade de Medicina da Bahia da Universidade Federal da Bahia,[1] Salvador, BA – Brazil
Hospital Universitário Professor Edgard Santos,[2] Salvador, BA – Brazil

Abstract

Background: Cardiovascular disease is the main cause of death worldwide. There is a lack of studies addressing this issue in women and its risk factors, such as hypertension.

Objective: To evaluate the clinical and therapeutic profile of women with hypertension and to determine which factors are related to treatment adherence and blood pressure control.

Methods: Cross-sectional study of 181 hypertensive women treated at an outpatient referral clinic. Data were obtained from medical records, face-to-face interviews, and physical examination, using a standardized form. Statistical analysis was performed with prevalence ratio, chi-square and Student's t test. Significance was accepted at $p<0.05$.

Results: Most patients were mixed-race or black (91.7%) and the mean age was 66.09 years. Only 44.2% of patients had controlled blood pressure. The prevalence of stroke was 14.9%, whereas the prevalence of coronary artery disease was 19.3%. The mean number of oral antihypertensive drugs prescribed to each individual was 3.41. A history of stroke was more often found in patients with uncontrolled blood pressure ($p=0.013$) and in those using three or more antihypertensives ($p=0.023$). Eighty patients (44.2%) had high treatment adherence. Depression was more frequently reported by patients with poorer adherence to treatment ($p=0.026$).

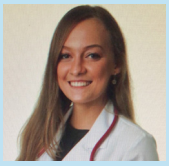
Conclusion: Women with hypertension presented a high prevalence of cardiovascular risk factors and cardiovascular events, including a significantly higher prevalence of stroke in those with uncontrolled hypertension. Self-reported depression may help identify patients at risk of nonadherence to treatment.

Keywords: Women; Hypertension; Medication Adherence; Antihypertensive Agents; Blood Pressure.

Introduction

Cardiovascular disease (CVD) is the leading cause of death worldwide. For many years, it was believed that CVD was much more prevalent in men, probably due to the lack of studies that addressed this issue in women and their risk factors, according to their biological particularities.[1] Cardiovascular risk factors common to both genders have been identified. However, some studies have shown that these factors are associated with worse outcomes in women in comparison to men.[2-4] In general, women usually develop CVD 10 years later than men, so that the prevalence of CVD increases in the postmenopausal period, probably due to the decline in estrogen hormone levels.[5]

There is little difference in the prevalence of arterial hypertension between genders, but previous studies have shown that women tend to receive less aggressive



Júlia Lasserre Moreira
Medical Student
Universidade Federal da Bahia - UFBA

Mailing Address: Pedro Henrique Barletta
Largo Terreiro de Jesus, s/n. Postal Code: 40026-010, Pelourinho, Salvador, BA – Brazil.
E-mail: pedro.barletta@hotmail.com

DOI: https://doi.org/10.36660/ijcs.20200417

Manuscript received December 30, 2020; revised manuscript March 17, 2021; accepted May 27, 2021.

antihypertensive treatment than men.[6] This finding may be related to therapeutic inertia in the approach to women or poor adherence to antihypertensive treatment, which may lead to increased cardiovascular morbidity and mortality.[7]

Despite knowledge about gender differences in arterial hypertension management and prevalence of CVD, these relations are still insufficiently understood, especially in the Brazilian population. Given the lack of studies focused on the clinical management of arterial hypertension in women, our objective was to evaluate the clinical and therapeutic profile of women followed at a referral outpatient clinic for arterial hypertension and to determine which factors were associated with treatment adherence and blood pressure control.

Methods

This was a descriptive, cross-sectional study carried out in an outpatient referral clinic for Severe Hypertensive Cardiovascular Disease at a university hospital in the city of Salvador, Bahia. The study included a convenience sample of female patients with a previous diagnosis of hypertension, aged 18 years or older, followed at the aforementioned clinic, between June 2018 and February 2020. Patients unable to respond to the questionnaire were excluded.

Information was obtained by trained raters through face-to-face interviews, physical examination, and a review of medical records. A standard form approved by the institution's Research Ethics Committee was used. All patients agreed to participate in the study and signed a free and informed consent form.

Patients were referred to a treatment room, where they were asked to remain seated and answered questions on their life habits, medical history, therapeutic scheme used, and adherence to the proposed treatment. After a few minutes, blood pressure was measured using a digital sphygmomanometer (BP785, Omron Healthcare). The patients were instructed to sit with their backs against the chair, feet uncrossed and on the floor. They were also instructed to empty their bladder before the measurement. There was a minimum interval of 30 minutes between the intake of caffeinated beverages and smoking and the measurement, as well as 60 minutes between physical exercise and blood pressure measurement.

The arm was positioned extended, at the height of the heart, and after palpation of the brachial artery, the cuff was positioned 3 centimeters above the cubital fossa. For obese patients, a suitable cuff with a larger circumference was used (HEMCL24, Omron Healthcare). The measurement was performed in both arms, with an interval of at least 1 minute between measurements. Of these two measurements, the one with the highest mean arterial pressure [(2 x diastolic blood pressure + systolic blood pressure) / 3] was considered for the analysis.

Patients with uncontrolled blood pressure (BP) despite the use of ≥ 3 antihypertensive drugs with synergistic actions, at maximum recommended or tolerated doses, or those with BP controlled only with ≥ 4 antihypertensive drugs were considered to have apparent resistant hypertension (RH).[8] Uncontrolled hypertension was defined as a systolic blood pressure ≥ 140 mmHg or diastolic blood pressure ≥ 90 mmHg.[8]

To assess medication adherence, the 8-item Morisky Medication Adherence Scale (MMAS-8) was used. Individuals with scores of 8, 7 - 6 and ≤ 5 were classified as having high, moderate, and low therapeutic adherence, respectively. Patients who had high adherence were considered adherent to treatment, while patients with moderate and low adherence were classified as nonadherent.

Information about the pharmacological prescriptions of each individual was obtained from medical records. Serum potassium (K^+) and serum creatinine (Cr) levels were also obtained from medical records, to search for a possible rationale for not using drugs known to induce hyperkalemia. The presence of previous cardiovascular events (such as stroke and acute myocardial infarction) or comorbidities (heart failure, coronary artery disease, diabetes, dyslipidemia) was defined by a positive history reported by the participant and/or noted in the medical record.

The glomerular filtration rate (GFR) was estimated using the Chronic Kidney Disease Epidemiology Collaboration group (CKD-EPI) equation.[9] Renal function was considered abnormal when GFR <60 mL/min. Obesity was defined as a body mass index (BMI) greater than 30 kg/m².

Depression was defined by a self-reported previous medical diagnosis of major depression in need of pharmacological antidepressant therapy. Sedentary lifestyle was defined as self-reported physical inactivity

or less than 150 minutes of physical activity per week. Difficulty in replacing medications, alcohol use, and smoking were all based on self-report.

Statistical Analysis

Statistical analysis was performed in SPSS, Version 23.0. Categorical variables were presented as absolute and relative frequencies, while continuous variables were presented as means and standard deviations (SD). The relative frequencies were presented as valid percentages. The chi-square (χ^2) statistic and prevalence ratio (PR) were used to investigate associations. The Kolmogorov-Smirnov test was used to certify the normality of the data distribution. The comparison of means was performed using Student's *t* test for independent samples. The mean blood pressure values obtained were compared with the target blood pressure levels of 140/90 mmHg using the one-sample *t* test. Statistical significance was established at $p < 0.05$, two-tailed.

Ethical Considerations

This study was approved by the Research Ethics Committee of *Hospital Universitário Professor Edgard Santos, Universidade Federal da Bahia*, on April 25, 2018. In accordance with Brazilian National Health Council Resolution No. 466/2012 on research involving human beings, the study protocol was registered on the Plataforma Brasil website (CAAE number 81701717.6.0000.0049). All authors signed a data use agreement. The standardized form used to collect patient information was approved by the local institutional review board.

Results

The sample consisted of 181 patients. Of these, 103 (57.5%) self-identified as black, 63 (35.2%) as mixed-race, and 10 (5.6%) as white. The mean age of patients was 66.09 years (± 10.44), with a minimum age of 39 and maximum of 87 years. The mean systolic blood pressure (SBP) was 146.93 (± 25.67) mmHg ($p < 0.001$). The mean diastolic blood pressure (DBP) was 83.09 (± 13.45) mmHg ($p < 0.001$). Table 1 presents the main comorbidities of the patients.

Only 44.2% of patients had controlled blood pressure. One hundred and ten (60.8%) were considered to have apparent RH. Regarding therapeutic adherence, the mean score on the MMAS-8 scale was 6.85 (± 1.52) points, and the percentage of individuals with low therapeutic adherence was 13.8%; moderate adherence, 42.0%; and high adherence, 44.2%.

Table 1 presents the PR values of the independent variables in relation to blood pressure control. A history of stroke was more often found in patients with uncontrolled BP (p=0.013), who also took more antihypertensive drugs in comparison to patients with controlled BP (p=0.023). There was no statistical difference in the mean score on the MMAS-8 scale between patients with and without a previous stroke (6.67 vs 6.88, p=0.509), and no difference in adherence was noted between the group of individuals using 3 or more drugs and the group using fewer than 3 drugs (6.87 vs 6.75, p=0.654).

Regarding the medication profile (Table 2), the mean number of oral antihypertensive drugs taken by each individual was 3.41 (± 1.20). Antihypertensive monotherapy was prescribed only to 2.2% of patients; 19.9% were taking two antihypertensive drugs; 35.4% were taking three drugs, whereas the remaining 42.5% of the patients were on four or more drugs. Twenty-four patients (13.3%) had uncontrolled blood pressure despite use of five or more antihypertensive drugs.

Considering only those patients with apparent RH, 71.56% of these individuals were on a therapeutic regimen consisting of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) + diuretic + calcium channel blocker (CCB). Among these individuals, considering those who needed 4 or more antihypertensive drugs, a beta-blocker was the most commonly prescribed fourth drug (63.6%), whereas 58.2% of the patients took spironolactone. In this same group of patients, the mean $[K^+]$ of those who did not take spironolactone was 4.13 (± 0.55) mmol/L, versus 4.51 (± 0.39) mmol/L in those who did, a statistically significant difference (p=0.028). The mean serum creatinine level among those who did not take spironolactone and those who did was, respectively, 0.92 (± 0.20) mg/dL and 0.90 (± 0.24) mg/dL, with no significant difference (p=0.857).

Patients who were on four or more antihypertensive drugs had a higher prevalence of coronary artery disease (CAD) (27.3% vs 13.5%, p=0.020), previous myocardial infarction (MI) (20.8% vs 9.6, p=0.034), and heart failure (HF) (19.7% vs 8.7%, p=0.033) in comparison to those who took three or fewer antihypertensives.

Of the patients with uncontrolled blood pressure despite the use of 5 or more antihypertensive drugs,

Table 1 – Variables in relation to blood pressure control

Variable	Regarding to the total sample	Controlled BP (n = 79)	Uncontrolled BP (n = 101)	PR	95% confidence interval	p-value
Age (years)	66.09 (± 10.44)	64.83 (± 10.09)	67.10 (± 10.66)	-	-	0.146
Number of drugs used	3.41 (± 1.20)	3.09 (± 1.12)	3.66 (± 1.20)	-	-	0.001
SBP (mmHg)	146.93 (± 25.67)	125.61 (± 11.34)	163.81 (± 20.80)	-	-	< 0.001
DBP (mmHg)	83.09 (± 13.45)	76.26 (± 8.83)	88.50 (± 14.03)	-	-	< 0.001
Years of follow-up at the clinic	15.12 (± 8.89)	15.50 (± 9.90)	14.82 (± 8.06)	-	-	0.612
Years of schooling	7.93 (± 4.17)	8.15 (± 3.90)	7.75 (± 4.38)	-	-	0.526
Years since diagnosis of hypertension	24.50 (± 11.40)	23.84 (± 11.84)	25.05 (± 11.07)	-	-	0.486
African descent	166 (91.7%)	73 (91.3%)	93 (92.1%)	0.942	0.534 – 1.662	0.841
Obesity (BMI > 30 kg/m²)	73 (41.7%)	36 (45.6%)	37 (38.5%)	1.170	0.845 - 1.619	0.348
Sedentary lifestyle	85 (47.0%)	39 (48.8%)	46 (45.5%)	1.074	0.775 - 1.490	0.668
Difficulty in replacing medications	31 (23.8%)	16 (28.1%)	15 (20.5%)	1.246	0.824 - 1.885	0.318
Alcoholism	38 (21%)	20 (25.0%)	18 (17.8%)	1.254	0.877 - 1.794	0.239
Current smoking	6 (3.3%)	4 (5.0%)	2 (2.0%)	1.535	0.850 - 2.771	0.260
On three or more antihypertensives	141 (77.9%)	56 (70.0%)	85 (84.2%)	0.662	0.478 - 0.916	0.023
HF	24 (13.4%)	15 (18.8%)	9 (9.1%)	1.490	1.039 - 2.138	0.059
CAD	35 (19.3%)	13 (16.3%)	20 (21.8%)	0.809	0.508 - 1.289	0.349
CKD	27 (17.8%)	11 (15.7%)	16 (19.5%)	0.863	0.528 - 1.411	0.541
Diabetes	87 (48.1%)	36 (45.0%)	51 (50.5%)	0.884	0.635 - 1.230	0.462
Dyslipidemia	139 (77.7%)	65 (82.3%)	74 (74.0%)	1.336	0.845 - 2.112	0.187
Stroke	27 (14.9%)	6 (7.5%)	21 (20.8%)	0.462	0.224 - 0.954	0.013
Self-reported depression	41 (22.8%)	18 (22.8%)	23 (22.8%)	1.000	0.675 - 1.483	0.998

Categorical variables were represented as n (valid %) and the p-values were obtained from the chi-square test;
Continuous variables were represented as mean (± SD) and the p-values were obtained from the Student's t test;
BP: blood pressure; CAD: coronary artery disease; HF: heart failure; BMI: body mass index; CKD: chronic kidney disease; PR: prevalence ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure.

20.8% did not take spironolactone, and 54.2% did not take the combination of chlortalidone and spironolactone.

Table 3 shows the PR values of the independent variables and the comparison of the means of the continuous variables in relation to treatment adherence. Comparing the treatment-adherent group (MMAS-8 = 8) to the nonadherent group (MMAS-8 ≤ 7) revealed that depression was more frequently reported by patients with poorer adherence to treatment (p=0.026). There was no statistically significant difference in mean age, number of drugs taken, or mean pressure levels. There was no significant impact of number of years of follow-up at the clinic, education level, and time since diagnosis of hypertension. There was no association between high therapeutic adherence and blood pressure control (p=0.653).

Table 2 – Antihypertensive drugs and percentage of use in the sample

Drugs	Percentage of individuals using the drug	HTN	Apparent RH
	(N=181)	(N=71)	(N= 110)
Thiazide diuretics	81.2%	73.3%	86.4%
Hydrochlorothiazide	54.1%	59.2%	50.9%
Chlortalidone	25.4%	11.3%	34.5%
Indapamide	1.7%	2.8%	0.9%
Other diuretics			
Spironolactone	28.2%	1.4%	45.5%
Furosemide	6.6%	1.4%	10.0%
ACEI/ARB	98.9%	98.6%	99.1%
Losartan	70.7%	71.8%	70.0%
Enalapril	23.2%	22.5%	23.6%
Captopril	0.6%	1.4%	0.0%
CCB	70.2%	52.1%	81.8%
Amlodipine	68%	50.7%	79.1%
Nifedipine	2.2%	1.4%	2.7%
Beta-blocker	36.5%	11.3%	52.7%
Carvedilol	18.8%	1.4%	30.0%
Atenolol	11.0%	5.6%	14.5%
Propranolol	3.9%	1.4%	5.5%
Metoprolol	3.3%	2.8%	3.6%
Direct vasodilators	5.5%	0.0%	9.1%
Central alpha-agonists	10.5%	0.0%	17.3%

ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin II receptor blocker; CCB: calcium channel blocker; HTN: arterial hypertension; RH: resistant hypertension.

Discussion

This study analyzed the clinical characteristics of 181 female hypertensive patients followed at an outpatient referral clinic for severe hypertension. We observed a high prevalence of concomitant risk factors for CVD, including dyslipidemia (78%), diabetes mellitus (48%), and obesity (42%), as previously described in patients with RH.[10] However, we found a lower prevalence of current smoking (3%), probably reflecting sex differences in the prevalence of traditional cardiovascular risk factors.[11] In a previous study involving hypertensive patients followed in primary health care centers in Portugal (the PRECISE study), the prevalence of cardiovascular comorbidities in women was similar to that found in our sample, especially for dyslipidemia, current smoking, and obesity, in addition to similar rates of uncontrolled hypertension.[12] Thus, the frequency of cardiovascular comorbidities in our sample was similar to that described in other countries.

Considering cardiovascular events, we found a significantly higher prevalence of stroke in patients with uncontrolled hypertension, who also took more antihypertensive drugs in comparison to patients

Table 3 – Variables of interest and relation to therapeutic adherence

Variable	Adherent (n=80)	Nonadherent (n=101)	PR	95% confidence interval	p-value
Age (years)	67.03 (± 8.97)	65.36 (± 11.47)	-	-	0.274
Number of drugs used	3.31 (± 1.12)	3.49 (± 1.25)	-	-	0.336
SBP (mmHg)	146.33 (± 25.35)	147.40 (± 26.03)	-	-	0.782
DBP (mmHg)	82.60 (± 12.20)	83.48 (± 14.40)	-	-	0.665
Years of follow-up at the clinic	14.99 (± 8.78)	15.21 (± 9.02)	-	-	0.872
Years of schooling	7.65 (± 3.95)	8.15 (± 4.34)	-	-	0.426
Years since diagnosis of hypertension	22.88 (± 10.00)	25.85 (± 12.33)	-	-	0.085
African descent	75 (93.8%)	91 (90.1%)	1.355	0.650 – 2.827	0.376
Self-reported depression	12 (15.0%)	29 (29.0%)	0.598	0.361 - 0.992	0.026
HF	8 (10.3%)	16 (15.8%)	0.738	0.408 - 1.334	0.277
CAD	15 (18.8%)	20 (19.8%)	0.963	0.630 - 1470	0.859
Obesity (BMI > 30 kg/m2)	38 (48.7%)	35 (36.1%)	1.327	0.957 - 1.841	0.092
CKD	16 (23.5%)	11 (13.1%)	1.425	0.979 - 2.074	0.094
Difficulty in replacing medications	10 (16.9%)	21 (29.6%)	0.652	0.377 - 1.127	0.093
Alcoholism	15 (18.8%)	23 (22.8%)	0.868	0.563 - 1.339	0.509
Diabetes	41 (51.2%)	46 (45.5%)	1.136	0.819 - 1.576	0.445
Dyslipidemia	62 (79.5%)	77 (76.2%)	1.115	0.731 - 1.701	0.605
Stroke	11 (13.8%)	16 (15.8%)	0.909	0.558 - 1.481	0.695
Controlled BP	37 (46.3%)	43 (42.6%)	1.086	0.783 – 1.507	0.621

Categorical variables were represented as n (valid %) and the p-values were obtained from the chi-square test;
Continuous variables were represented as mean (± SD) and the p-values were obtained from the Student's t test;
Patients with 8 points on the MMAS-8 scale were classified as adherent, whereas those scoring 7 points or less were classified as nonadherent.
CAD: coronary artery disease; HF: heart failure; BMI: body mass index; CKD: chronic kidney disease; PR: prevalence ratio; SBP: systolic blood pressure; DBP: diastolic blood pressure; BP: blood pressure.

with controlled BP. Notably, the frequency of other cardiovascular risk factors was similar in the two subgroups, suggesting that inadequate BP control, probably more than other risk factors, plays a pivotal role in the development of stroke in patients with hypertension.

According to the literature, poor drug adherence is a major cause of uncontrolled hypertension and may lead to pseudo-resistance.[13] In the present study, 44.2% of patients were considered highly adherent to antihypertensive treatment, whereas 13.8% had low adherence based on the MMAS-8 questionnaire. Oliveira-Filho *et al* [14] reported a much lower proportion of high adherence (19.7%) in 223 patients followed at primary care units, and Morisky *et al* [15] found that only 15.9% of patients followed at a hypertension clinic had high therapeutic adherence. The higher prevalence of adherence observed in our study could be explained, at least in part, by the fact that the patients were attending a referral clinic, where more emphasis was possibly placed on adherence. In addition, there is evidence that women are more likely to be aware of hypertension[16] and to make better use of healthcare services than men,[17] which could increase their motivation to adhere to antihypertensive treatment, even though a recent meta-analysis did not find definitive evidence for this.[18] Interestingly, high therapeutic adherence did not relate to BP control in our

study. This finding may suggest that a significant number of patients were truly resistant to treatment.

In our sample, as in other studies,[19] there was a high prevalence of depression (23%) among women with hypertension. Comorbid major depression is three times more common in psychiatric outpatients with hypertension than in those without hypertension, an aspect that may be aggravated by sex differences, since depression is twice as prevalent in women as in men.[20,21] Furthermore, depressive symptoms may be related to a decline in medication adherence among hypertensive patients, a finding also observed in our study and consistent with the literature.[22,23] In fact, depressive symptoms are associated with reduced functioning and may also mediate the patient's self-perception of performing a specific activity (expectation of self-efficacy), leading the individual to make less effort to follow the prescribed recommendations and amplifying possible obstacles to medication adherence.[23,24] In addition, in a previous study involving patients with depressive disorder and low social support, women of African descent (which in our sample represented almost 95% of the patients) were less likely to adhere to depression treatment when compared to white males and females.[25] This finding may possibly indicate a low therapeutic adherence for other clinical comorbidities, such as hypertension.

In this regard, due to the high prevalence of comorbid depression in hypertension and its clinical implications for therapeutic adherence, it is important to reinforce the importance of recognition and screening of mood disorders in hypertensive patients, especially in women of African descent.

Regarding drug therapy regimens, we found that diuretics were the most commonly prescribed medications, followed by ARB and CCB. These results corroborate the findings of a previous meta-analysis, which observed that women more frequently used diuretics for treatment of hypertension, whereas men more often used beta-blockers, ACEI, and CCB.[26] A possible explanation for the preference of diuretics may be the side effects of some hypertensive medications, which affect women more often than men. Indeed, women experience a higher frequency of dry cough when taking ACEI, in addition to a higher incidence of edema and vasodilatation symptoms with CCB compared to men.[27,28] Despite these differences in therapeutic profile between genders, there is no evidence that blood pressure-lowering regimens (based on ACEI, CCB, ARB, or diuretics/beta-blockers) provide different levels of protection against major cardiovascular events in men and women.[29]

As recommended in the literature,[8] we observed that a large proportion of patients with apparent RH used the combination of a thiazide diuretic, a long-acting CCB, and a renin-angiotensin system blocker, which is the preferable regimen for resistant hypertension. Moreover, the addition of spironolactone was observed in most patients who needed four or more antihypertensive drugs. This represents a significant increase in the number of spironolactone prescriptions compared to previous studies,[30] probably reflecting the increasing recognition of its efficacy in RH as documented by several reports, particularly the PATHWAY-2 trial.[31] Nevertheless, the most common addition to the triple ACEI/ARB + diuretic + CCB regimen was a beta-blocker (63.6%), which could be justified by the high prevalence of CAD, previous MI, and HF in these patients.

On the other hand, only one-fourth of the women were on chlortalidone, despite recommendations in the literature supporting its use, especially in RH.[32] This is probably due to the fact that the study was conducted at a public clinic and chlortalidone is not covered by the Brazilian public health system. This also raises concerns about the prevalence of refractory hypertension, given the current definition of this phenotype, which requires the inclusion of spironolactone and a long-acting thiazide-like diuretic, such as chlorthalidone, in the therapeutic regimen.[8,33] Among the 24 patients with uncontrolled blood pressure despite the use of 5 or more antihypertensive drugs, only 11 (45.8%) were receiving the combination of spironolactone and chlorthalidone and could possibly meet the criteria for refractory hypertension. Future studies will need to clarify how the prevalence of refractory hypertension changes with the implementation of diuretic optimization in a higher proportion of patients.

Our study has some limitations. First, its cross-sectional design precludes causal inference between the associations found. Second, we used the MMAS-8 questionnaire to assess therapeutic adherence, which, despite being widely used, has limited accuracy in detecting nonadherence.[34] Third, we could not exclude the white-coat effect as a cause of pseudo-resistance in some patients. However, these patients were followed at a specialized hypertension clinic with a mean follow-up greater than 10 years, which could minimize the prevalence of pseudo-resistance in this population.

Another point is that, despite current recommendations for BP measurement,[8] we did not use the average of two measurements obtained in the arm with the highest BP levels as the reference value for the patient's BP. Instead, two measurements were performed, one in each arm, and the measurement with the highest mean arterial pressure was considered for analysis. Finally, the assessment of depression was based exclusively on patient self-report, with no specific instrument being applied for the diagnosis or measurement of the intensity of depressive symptoms.

Despite these limitations, our study also has strengths. To our knowledge, few studies were conducted with the aim of evaluating the clinical and therapeutic profile of hypertension exclusively in women in Brazil. Finally, the present study involved a sample of predominantly African descent, thus contributing to improved knowledge of the presentation and management of hypertension in this population.

Conclusions

In conclusion, in a sample of women with hypertension, we found a high prevalence of comorbid cardiovascular risk factors and previous cardiovascular events. Stroke was more often found in women with uncontrolled blood pressure levels, even though these patients were on more antihypertensive drugs, and self-reported depression was significantly associated with nonadherence. The therapeutic profile revealed that most patients were on three or more antihypertensive drugs; however, very few of them were taking a long-acting thiazide-like diuretic for resistant hypertension. Taken together, our findings reinforce the importance of conducting studies exclusively with women with hypertension in order to improve treatment adherence, blood pressure control, and clinical outcomes in this specific population.

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 *Hospital Universitário Professor Edgard Santos* under the protocol number 81701717.6.0000.0049. 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.

Author contributions

Conception and design of the research: Macedo CRB, Aras-Jr R. Acquisition of data: Barletta PHAAS, Magalhães EFS, Almeida VF, Moreira JL, Silva MJ. Analysis and interpretation of the data: Barletta PHAAS, Magalhães EFS, Almeida VF. Statistical analysis: Barletta PHAAS, Almeida VF. Writing of the manuscript: Barletta PHAAS, Magalhães EFS, Almeida VF, Moreira JL, Silva MJ. Critical revision of the manuscript for intellectual content: Barletta PHAAS, Magalhães EFS, Almeida VF, Moreira JL, Silva MJ, Macedo CRB, Aras-Jr R.

References

1. Appelman Y, van Rijn BB, Ten Haaf ME, Boersma E, Peters SA. Sex differences in cardiovascular risk factors and disease prevention. Atherosclerosis. 2015;241(1):211-8. doi: 10.1016/j.atherosclerosis.2015.01.027.
2. Millett ERC, Peters SAE, Woodward M. Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants. BMJ. 2018;363:k4247. doi: 10.1136/bmj.k4247.
3. Peters SA, Huxley RR, Woodward M. Diabetes as a risk factor for stroke in women compared with men: a systematic review and meta-analysis of 64 cohorts, including 775,385 individuals and 12,539 strokes. Lancet. 2014;383(9933):1973-80. doi: 10.1016/S0140-6736(14)60040-4.
4. Li X, Li X, Lin H, Fu X, Lin W, Li M, et al. Metabolic syndrome and stroke: a meta-analysis of prospective cohort studies. J Clin Neurosci. 2017;40:34-8. doi: 10.1016/j.jocn.2017.01.018.
5. Masjedi S, Ferdous Z. Understanding the role of sex in heart valve and major vascular diseases. Cardiovasc Eng Technol. 2015;6(3):209-19. doi: 10.1007/s13239-015-0226-x.
6. Smith SM, Huo T, Johnson BD, Bittner V, Kelsey SF, Thompson DV, et al. Cardiovascular and mortality risk of apparent resistant hypertension in women with suspected myocardial ischemia: a report from the NHLBI-sponsored WISE study. J Am Heart Assoc. 2014;3(1):e000660. doi: 10.1161/JAHA.113.000660.
7. Adigun RO, Boler AN, Mankad R. Disparities in cardiac care of women: current data and possible solutions. Curr Treat Options Cardiovasc Med. 2018;20(11):87. doi: 10.1007/s11936-018-0688-x.
8. Barroso WKS, Rodrigues CIS, Bortolotto LA, Mota-Gomes MA, Brandão AA, Feitosa ADM, et al. Brazilian Guidelines of Hypertension - 2020. Arq Bras Cardiol. 2021;116(3):516-658. doi: 10.36660/abc.20201238.

9. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12. doi: 10.7326/0003-4819-150-9-200905050-00006.

10. Chedier B, Cortez AF, Roderjan CN, Cavalcanti AH, Carlos FOC, Santos BDM, et al. Prevalence and clinical profile of refractory hypertension in a large cohort of patients with resistant hypertension. J Hum Hypertens. 2020. doi: 10.1038/s41371-020-00406-2.

11. Tziomalos K, Giampatzis V, Baltatzi M, Efthymiou E, Psianou K, Papastergiou N, et al. Sex-specific differences in cardiovascular risk factors and blood pressure control in hypertensive patients. J Clin Hypertens. 2014;16(4):309-12. doi: 10.1111/jch.12289.

12. Silva PM, Lima MJ, Neves PM, Macedo ME. Prevalence of cardiovascular risk factors and other comorbidities in patients with hypertension in Portuguese primary health care populations: The PRECISE study. Rev Port Cardiol. 2019;38(6):427-37. doi: 10.1016/j.repc.2018.09.011.

13. Oparil S, Acelajado MC, Bakris GL, Berlowitz DR, Cífková R, Dominiczak AF, et al. Hypertension. Nat Rev Dis Primers. 2018;4:18014. doi: 10.1038/nrdp.2018.14.

14. Oliveira-Filho AD, Barreto-Filho JA, Neves SJ, Lyra DP Jr. Association between the 8-item Morisky Medication Adherence Scale (MMAS-8) and blood pressure control. Arq Bras Cardiol. 2012;99(1):649-58. doi: 10.1590/s0066-782x2012005000053.

15. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence measure in an outpatient setting. J Clin Hypertens. 2008;10(5):348-54. doi: 10.1111/j.1751-7176.2008.07572.x.

16. Chor D, Ribeiro ALP, Carvalho MS, Duncan BB, Lotufo PA, Nobre AA, et al. Prevalence, awareness, treatment and influence of socioeconomic variables on control of high blood pressure: results of the ELSA-Brasil study. PLoS One. 2015;10(6):e0127382. doi: 10.1371/journal.pone.0127382.

17. Hong SH. Potential for physician communication to build favorable medication beliefs among older adults with hypertension: A cross-sectional survey. PLoS One. 2019;14(1):e0210169. doi: 10.1371/journal.pone.0210169.

18. Biffi A, Rea F, Iannaccone T, Filippelli A, Mancia G, Corrao G. Sex differences in the adherence of antihypertensive drugs: a systematic review with meta-analyses. BMJ Open. 2020;10(7):e036418. doi: 10.1136/bmjopen-2019-036418.

19. Li Z, Li Y, Chen L, Chen P, Hu Y. Prevalence of depression in patients with hypertension: a systematic review and meta-analysis. Medicine. 2015;94(31):e1317. doi: 10.1097/MD.0000000000001317.

20. Rabkin JG, Charles E, Kass F. Hypertension and DSM-III depression in psychiatric outpatients. Am J Psychiatry. 1983;140(8):1072-4. doi: 10.1176/ajp.140.8.1072.

21. Mauvais-Jarvis F, Merz NB, Barnes PJ, Brinton RD, Carrero JJ, DeMeo DL, et al. Sex and gender: modifiers of health, disease, and medicine. Lancet. 2020;396(10250):565-82. doi: 10.1016/S0140-6736(20)31561-0.

22. Krousel-Wood M, Joyce C, Holt E, Muntner P, Webber LS, Morisky DE, et al. Predictors of decline in medication adherence: results from the cohort study of medication adherence among older adults. Hypertension. 2011;58(5):804-10. doi: 10.1161/HYPERTENSIONAHA.111.176859.

23. Bautista LE, Vera-Cala LM, Colombo C, Smith P. Symptoms of depression and anxiety and adherence to antihypertensive medication. Am J Hypertens. 2012;25(4):505-11. doi: 10.1038/ajh.2011.256.

24. Son YJ, Won MH. Depression and medication adherence among older Korean patients with hypertension: mediating role of self-efficacy. Int J Nurs Pract. 2017;23(3). doi: 10.1111/ijn.12525.

25. Gerlach LB, Kavanagh J, Watkins D, Chiang C, Kim HM, Kales HC. With a little help from my friends?: racial and gender differences in the role of social support in later-life depression medication adherence. Int Psychogeriatr. 2017;29(9):1485-93. doi: 10.1017/S104161021700076X.

26. Klungel OH, de Boer A, Paes AH, Seidell JC, Bakker A. Sex differences in the pharmacological treatment of hypertension: a review of population-based studies. J Hypertens. 1997;15(6):591-600. doi: 10.1097/00004872-199715060-00004.

27. Muiesan ML, Salvetti M, Rosei CA, Paini A. Gender differences in antihypertensive treatment: myths or legends? High Blood Press Cardiovasc Prev. 2016;23(2):105-13. doi: 10.1007/s40292-016-0148-1.

28. Song JJ, Ma Z, Wang J, Chen LX, Zhong JC. Gender differences in hypertension. J Cardiovasc Transl Res. 2020;13(1):47-54. doi: 10.1007/s12265-019-09888-z.

29. Turnbull F, Woodward M, Neal B, Barzi F, Ninomiya T, Chalmers J, et al. Do men and women respond differently to blood pressure-lowering treatment? Results of prospectively designed overviews of randomized trials. Eur Heart J. 2008;29(21):2669-80. doi: 10.1093/eurheartj/ehn427.

30. Hwang AY, Dave C, Smith SM. Trends in antihypertensive medication use among US patients with resistant hypertension, 2008 to 2014. Hypertension. 2016;68(6):1349-54. doi: 10.1161/HYPERTENSIONAHA.116.08128.

31. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015;386(10008):2059-68. doi: 10.1016/S0140-6736(15)00257-3.

32. Acelajado MC, Hughes ZH, Oparil S, Calhoun DA. Treatment of resistant and refractory hypertension. Circ Res. 2019;124(7):1061-70. doi: 10.1161/CIRCRESAHA.118.312156.

33. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Himmelfarb CD, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association task force on clinical practice guidelines. Hypertension. 2018;71(6):13-115. doi: 10.1161/HYP.0000000000000065.

34. Pandey A, Raza F, Velasco A, Brinker S, Ayers C, Das SR, et al. Comparison of Morisky Medication Adherence Scale with therapeutic drug monitoring in apparent treatment-resistant hypertension. J Am Soc Hypertens. 2015;9(6):420-6.e2. doi: 10.1016/j.jash.2015.04.004.

EDITORIAL

Blood Pressure Control and Therapeutic Adherence – The Challenges of Hypertension

Elizabeth Silaid Muxfeldt[1,2]

Universidade Federal do Rio de Janeiro,[1] Rio de Janeiro, RJ – Brazil
Universidade Estácio de Sá,[2] Rio de Janeiro, RJ – Brazil

Editorial referring to the article: Clinical Characteristics and Therapeutic Adherence of Women in a Referral Outpatient Clinic for Severe Hypertension

Blood pressure control is the greatest challenge in the treatment of hypertension.[1,2] The control rate varies from 10% to 32% among continents, and it is related to the development level of each country, with averages ranging from 27% in low- and middle-income countries to 51% in high-income countries.[1] In Brazil, the rates of awareness (22% – 77%), treatment (11% – 78%), and blood pressure control (10% – 36%) also vary depending on the population studied.[3] Clinical inertia, inappropriate lifestyle, and poor therapeutic adherence are the main reasons for difficulty in reaching the therapeutic target.

Several factors affect adherence to treatment, including sociodemographic factors, as well as factors related to patients, drug treatment, and healthcare providers.[2,4] The main sociodemographic factors are age (younger and very elderly patients), poverty, ethnicity (minorities), and lack of social support. Few studies have assessed the difference in adherence between men and women, and they present controversial results.[5]

Regarding patient-related factors, denial of a silent disease such as hypertension and difficulty in understanding its severity and effectiveness of treatment for an asymptomatic condition are decisive to adherence. The emergence of symptoms as side effects of anti-hypertensive drugs may reduce adherence even more.[2,4,5]

Considering drug treatment, we know that the chronic use of medication leads to a progressive decrease in adherence, with reports showing that less than half of patients continue using medication regularly after a year of treatment.[4] Furthermore, the high number of drugs and complex therapeutic schemes make comprehension difficult and increase costs. In this sense, patients with resistant hypertension – those using three or more anti-hypertensive drugs, in addition to specific medication for comorbidities such as dyslipidemia and diabetes – deserve special attention, and they require constant adherence monitoring to avoid pseudo-resistance.[6] In a recent systematic review assessing 24 studies on patients with resistant hypertension, the prevalence of non-adherence was 31.2% (95% confidence interval = 20.2 – 44.7, I = 99.50), ranging from 3.3% to 86.1%.[7] This variation was directly related to the method used to evaluate adherence. Subjective self-report questionnaires show higher adherence than more objective methods.[7] The main variables associated with poor adherence among patients with resistant hypertension are female sex, physical inactivity, depressive symptoms, and history of coronary disease.[8]

Barletta et al. assessed 181 women with hypertension, 60.8% of whom were diagnosed with apparent resistant hypertension. The study found that 44.2% of patients had appropriate blood pressure control based on office measurement. Adherence was evaluated using the 8-item Morisky Medication Adherence Scale (MMAS-8), which showed that 13.8% had low adherence, 42.0%, moderate adherence, and 44.2%, high adherence. The variable independently related to low adherence was depression.[9] A systematic review and meta-analysis including 28 studies that also evaluated adherence using MMAS-8 found a 45% prevalence of non-adherence, with a risk 1.3 times higher among men.[10] This high rate of blood pressure control associated with moderate/high adherence (higher than 80%) is probably due to the follow-up of patients in a specialized hypertension care clinic. It is also the result of a subjective evaluation method

Keywords

Blood Pressure; Hypertension; Prevalence; Medication Adherence.

Mailing Address: Elizabeth Silaid Muxfeldt
Universidade Federal do Rio de Janeiro - Medical clinic
Rua Prof. Rodolpho Paulo Rocco, 255. Postal Code: 21941-901, Rio de Janeiro, RJ - Brazil.

DOI: https://doi.org/10.36660/ijcs.20210172

Elizabeth Silaid Muxfeldt, MD, PhD
Coordinator of the Arterial Hypertension Program - ProHArt - HUCFF - UFRJ
Coordinator of the LapARC Study - UNESA-RJ
Universidade Federal do Rio de Janeiro - UFRJ / Universidade Estácio de Sá - UNESA

of adherence and especially the female population of the study, usually more focused on self-care.

While several subjective and objective evaluation methods of therapeutic adherence exist, none of them are considered the gold standard. Therefore, this assessment is a complex task that is difficult to quantify.[2] Furthermore, it is difficult to establish a cut-off point for good adherence that is able to guarantee the benefits of anti-hypertensive treatment.[4] Among direct methods, there are blood or urine drug level measurements and digital medicines (ingestible sensors incorporated in the pill during the manufacturing process that generate a coded message after pill ingestion). Both are high-cost options, and they may be affected by biological factors.[2,4] Indirect methods include self-reporting scales, doctors' impressions, evaluation of clinical response, and manual counting of pills. All methods have low sensitivity and are susceptible to errors. There are also electronic devices to monitor the use of drugs. Although they are very accurate, this is also a high-cost alternative.[2,4]

Thus, it is essential to develop strategies capable of promoting better therapeutic adherence, with the goal of an effective reduction in cardiovascular morbimortality through blood pressure control. These strategies should focus on the patient, the drug treatment, and healthcare providers.[2]

Healthcare education to develop awareness, self-care promotion, family and social support, and home blood pressure monitoring are some of the actions that may be taken to increase adherence. Recent studies have been using telemonitoring, although this method is still expensive and difficult to access.[2,4] Other actions include the prescription of less complex therapeutic schemes, with long-acting drugs (reducing the number of daily pills) with fewer side effects, the combination of drugs in a single pill, and increased access to drugs through public policies for the distribution of free or low-cost medication. Furthermore, it is necessary to encourage the creation of multidisciplinary teams that are capable of guiding, prescribing, monitoring, and proposing effective changes in lifestyle and self-care.

References

1. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, et al. Global Disparities of Hypertension Prevalence and Control: A Systematic Analysis of Population-Based Studies from 90 Countries. Circulation. 2016;134(6):441-50. doi: 10.1161/CIRCULATIONAHA.115.018912.
2. Barroso WKS, Rodrigues CIS, Bortolotto LA, Mota-Gomes MA, Brandão AA, Feitosa ADM, et al. Brazilian Guidelines of Hypertension - 2020. Arq Bras Cardiol. 2021;116(3):516-658. doi: 10.36660/abc.20201238.
3. Scala LC, Magalhães LB, Machado A. Epidemiologia da Hipertensão Arterial Sistêmica. In: Moreira SM, Paola AV; Sociedade Brasileira de Cardiologia. Livro Texto da Sociedade Brasileira de Cardiologia. 2nd ed. São Paulo: Manole; 2015. p. 780-5.
4. Burnier M, Egan BM. Adherence in Hypertension. Circ Res. 2019;124(7):1124-40. doi: 10.1161/CIRCRESAHA.118.313220.
5. Dhar L, Dantas J, Ali M. A systematic Review of Factors Influencing Medication Adherence to Hypertension Treatment in Developing Countries. Open J Epidemiol. 2017;7(3):211-50. doi:10.4236/ojepi.2017.73018.
6. Yugar-Toledo JC, Moreno H Jr, Gus M, Rosito GBA, Scala LCN, Muxfeldt ES, et al. Posicionamento Brasileiro sobre Hipertensão Arterial Resistente – 2020. Arq Bras Cardiol. 2020; 114(3):576-96. doi: 10.36660/abc.20200198.
7. Durand H, Hayes P, Morrissey EC, Newell J, Casey M, Murphy AW, et al. Medication Adherence Among Patients with Apparent Treatment-Resistant Hypertension: Systematic Review and Meta-Analysis. J Hypertens. 2017;35(12):2346-57. doi: 10.1097/HJH.0000000000001502.
8. Irvin MR, Shimbo D, Mann DM, Reynolds K, Krousel-Wood M, Limdi NA, et al. Prevalence and Correlates of Low Medication Adherence in Apparent Treatment-Resistant Hypertension. J Clin Hypertens. 2012;14(10):694-700. doi: 10.1111/j.1751-7176.2012.00690.x.
9. Barletta PH, Magalhães EFS, Almeida VF, Moreira JL, Silva MJ, Macedo MJ, et al. Clinical Characteristics and Therapeutic Adherence of Women in a Referral Outpatient Clinic for Severe Hypertension. Int J Cardiovasc Sci. 2021; 34(4):400-408. doi: 10.36660/ijcs.20200417.
10. Abegaz TM, Shehab A, Gebreyohannes EA, Bhagavathula AS, Elnour AA. Nonadherence to Antihypertensive Drugs: A Systematic Review and Meta-Analysis. Medicine. 2017;96(4):5641. doi: 10.1097/MD.0000000000005641.

ORIGINAL ARTICLE

DD Genotype and Atherosclerosis in Overweight Menopausal Women

José Ramón Lanz-Luces,[1,2] Fernando Alves Costa,[2,3] Luis Fernando Escobar Guzman,[1,3] Antonio Ricardo de Toledo Gagliardi,[1] José Antonio Lanz-Luces,[2] José Daniel Lanz-Souquett,[2] Leandro Menezes Alves da Costa[2,4]

Universidade de São Paulo - Instituto do Coração,[1] São Paulo, SP – Brazil
Instituto Paulista de Doenças Cardiovasculares (IPDC),[2] São Paulo, SP – Brazil
Hospital Beneficência Portuguesa de São Paulo,[3] São Paulo, SP – Brazil
Hospital Alemão Oswaldo Cruz,[4] São Paulo, SP – Brazil

Abstract

Background: Sex-specific pathology of coronary artery disease (CAD) has not been recognized. Women with obstructive or nonobstructive CAD associated with traditional risk factors have similar events; no studies have explored both populations in association with genetic markers.

Objective: To evaluate the DD genotype in overweight menopausal women and its association with CAD and traditional risk factors.

Method: This cross-sectional study included 356 menopausal women who underwent coronary angiography as CAD assessment. The patients' DNA was extracted and polymorphisms were detected with a single polymerase chain reaction assay. Two groups were formed based on luminal lesions (normal [n = 134] or pathological [n = 222]) with a cutoff value > 30%, considering overweight and age. The chi-square test, Student's t-test, and multivariate logistic regression were performed as appropriate ($p < 0.05$) using the following variables: overweight, diabetes, hypertension, dyslipidemia, smoking status, sedentary lifestyle, and a family history of CAD.

Results: The mean age of the sample was 63 ± 8 years, and the mean BMI was 28 ± 5 kg/m^2. The DD genotype was slightly more prevalent in the pathological group (30.2% vs. 21.6%, p = 0.079), but this significantly changed when BMI > 25 was considered (33% vs. 18%, p = 0.012). In multivariate analysis with two threshold levels (> 50 and > 60 years), diabetes was significantly associated with CAD in both models (p = 0.021 vs. 0.009) but the genotype was only associated with younger age (p = 0.034).

Conclusion: These data support an association between atherosclerosis and the renin–angiotensin system in overweight menopausal women that is dependent on the age at which the ischemic event occurs.

Keywords: Overweight; Menopause; Coronary Artery Disease; Genetic Markers; DD Genotype.

Introduction

Menopause, a unique physiological stage that occurs in middle-aged women, involves important metabolic changes. One of these changes is an increase in low-density lipoprotein levels, which is sometimes associated with age at menopause onset.[1] In addition, lipid profile changes are strongly associated with coronary artery disease (CAD) in these women. This alteration has sometimes been attributed to the effects of hormone replacement on low-density lipoprotein particles.[2] Studies have emphasized that although estrogen therapy increases the levels of high-density lipoprotein and its components,[4] individual variability, which depends on allelic variants of the estrogen receptor gene, is also a factor.[3] A publication

José Ramón Lanz-Luces, MD, PhD
Research Assistant
Instituto Paulista de Doenças Cardiovasculares

Mailing Address: José Ramón Lanz-Luces
Rua Maestro Cardim, 560 - 10º andar, CJ 101 - Bela Vista - São Paulo - SP, 01323-001
E-mail: jrlanz2000@gmail.com

DOI: https://doi.org/10.36660/ijcs.20200400

Manuscript received October 08, 2020; revised manuscript February 03, 2021; accepted April 26, 2021.

by the Women's Health Group recommends limiting hormone replacement therapy in menopausal women due to the higher relative risk of CAD in a population that already had a high rate of CAD prior to enrolment.[5]

Recent studies have also investigated the role of adipose tissue, specifically its molecular mediators (eg, adipocytokines) in menopausal women.[6] Of note, obesity is common in menopausal women and increases inflammatory cytokine levels, integrating metabolic and inflammatory responses.[7] One of these concepts is derived from an observed association between the blockade of AT1 receptors and adiponectin expression.[8] Low levels of adiponectin are associated with higher levels of interleukin-6,[9] a molecule that is involved in atherosclerosis.[10] In addition, AT1 receptors in circulating macrophages play a role in angiotensin II-mediated cytokine production.[11]

There is a 287-base pair insertion/deletion polymorphism in the angiotensin-converting enzyme gene in intron 16, resulting in three genotypes; II, ID and DD. The latter is a linkage marker with therapeutic implications in cardiovascular disease.[12]

Clinically, the DD genotype has already been associated with endothelial dysfunction in postmenopausal women,[13] as well as with CAD. Amara et al,[14] found a significant prevalence of the DD genotype in a population with symptomatic CAD (odds ratio [OR] = 6.8, 95% confidence interval [CI]: 4.4–10, $p < 0.001$). The risk was greatly potentiated by several concomitant risk factors (smoking, diabetes, hypertension, dyslipidemia, and family history of CAD).

Considering this scenario, a better diagnostic method for classifying CAD risk is necessary. Based on existing evidence, the DD genotype increases the risk of CAD in younger individuals.[15] Moreover, a metabolic transition threshold is observed during the menopausal age.[16] We suggest that the polymorphism in this special condition, along with related factors, could be involved in atherosclerosis and can be evaluated using coronary angiography.

Materials and Methods

This was a retrospective, observational, analytic cross-sectional cohort single-center study (at the Heart Institute, University of São Paulo). Participants were selected from a database of 1449 patients during 2001 to 2003, (only one investigator was present at upon patient arrival for coronary angiogram and his availability depended on institutional hours). The investigator was available approximately 70% of the time at the hemodynamic laboratory to perform the optional coronary angiogram for the patients. Thus, a mixed sample design was selected to produce a representative sample and to surpass the minimum required sample size, using purposeful random sampling (random cases were selected from the sampling frame, alternating morning and afternoon tests), criterion sampling (only patients with suspected or proven CAD), and convenience sampling (in the chosen setting, groups and/or individuals who are conveniently available and willing to participate) as previously described.[17] From this database we selected 583 female patients, whose mean age was 63 $\pm$ 8 years (Table 1). The sample's clinical characteristics included the

Table 1 – Population characteristics

	General (356)	Normal (134) vs. Pathological (222)		p-value
Age (years)	63±8	61±8	65±8	<0.001
BMI (Kg/m²)	28±5	29±5.8	27±4.9	0.008
DM	128 (36%)	34(26.6%)	94(73.4%)	0.001
HT	288 (81%)	102(35.4%)	186(64.6%)	0.075
DLP	213 (59.8%)	76(35.7%)	137(64.3%)	0.352
SM	87 (24.4%)	32(36.8%)	55 (63.2%)	0.849
CAD hist.	255 (71.6%)	96 (37.6%)	159 (62.4%)	0.997
DD genotype	96 (27%)	29(30.2%)	67(69.8%)	0.079

BMI: Body Mass Index, DM: Diabetes, HT: Hypertension, DLP: Dyslipidemia, SM: smoking,CAD hist: family history of Coronary Artery Disease, first-degree relative <65 years. Continuous variables are expressed as mean and standard deviation, nominal variables are expressed as absolute value and percentage.

following variables: age, menopause (permanent cessation of ovulation) for at least 1 year.

Hypertension was defined as having been prescribed anti-hypertensive medications or blood pressure exceeding 140/90 mmHg. Diabetes was defined as hemoglobin a A1c value > 6.5% or fasting plasma glucose ≥ 126 mg/dl and/or the use of insulin or oral hypoglycemic agents. Dyslipidemia was defined according to laboratory results (total cholesterol ≥ 200 mg/dl, low-density lipoprotein cholesterol ≥ 130 mg/dl, high-density lipoprotein cholesterol < 40 mg/dl, triglycerides ≥ 150 mg/dl and/or hypolipidemic agent use), sedentary lifestyle, and a first-degree family history of CAD (< 65 years). Smoking was defined as daily or occasional self-reported cigarette consumption without having quit in the last year. Weight and height were assessed to determine body mass index (BMI), expressed as kg/m^2 (Table 1). A BMI > 25 Kg/m^2 was considered overweight.

Inclusion criteria

All patients underwent coronary catheterization to determine the presence of CAD, in addition to considering the presence of angina pectoris or the results of one of the following positive noninvasive tests: treadmill, echocardiogram with dobutamine, or cardiac scintigraphy. Some patients were asymptomatic, while others had adverse events such as unstable angina or myocardial infarction without previous coronary angiography. To be included, a patient had to provide all clinical data regarding the study variables (anthropometric measures and risk factors) and written informed consent prior to the coronary angiogram.

Exclusion criteria

Patients were excluded if they had previously undergone coronary angiography due to an ischemic event or if they were admitted to the hospital in an unstable condition.

Genotyping

An 8-mL peripheral blood sample was taken from each patient. The sample was stored in a tube containing ethylenediaminetetraacetic acid, and the DNA was obtained through the saline method. A polymerase chain reaction assay was performed to amplify the selected strain, using two primer kits for the insertion/deletion polymorphism of the angiotensin-converting enzyme gene (including an intronic pair), as described elsewhere. This was considered a *post-hoc* analysis from a previous study.[18]

Twenty coronary segments were examined to determine the presence of atherosclerosis. Epicardial vessels or main branches were divided into three segments (proximal, medial, and distal), except for secondary branches of the right coronary artery, which were divided into proximal and distal portions; this special classification was part of a previous study.[18] Patients were divided into two groups: those with and without lesions (ie, normal vs. pathological angiogram). A cutoff value of > 30% obstruction was established. The coronary angiogram threshold was considered non-significant from the point of view of obstructive angiography, but it established the presence of atherosclerosis. This cutoff value was derived from the Assessing Angiography Project as a lower range in visual assessment.[19] We also divided the population into groups according to BMI > or < 25 kg/m^2 and the presence or absence of CAD.

For logistic analysis, age was dichotomized as > 50 years or > 60 years, since: (1) studies have reported that the mean age of menopause onset ranges from 49–52 years,[20] and (2) the World Health Organization describes those aged ≥ 60 years as older adults.

This study was approved by the institutional ethics and research committee and was conducted in accordance with the most recent Declaration of Helsinki and World Medical Association guidelines. All patients provided written informed consent prior to participation. The study protocol did not interfere with any medical treatment and/or recommendations or other institutional protocols.

Statistical analyses

The sample size was calculated considering two groups for regression analysis and a power of 95%. A minimum of 119 patients were required for each group and a total of 234 cases. We used the Kolmogorov-Smirnov test to assess data normality. Continuous variables were expressed as means and standard deviations and categorical variables as absolute values and percentages. To assess the difference between the groups, we used the chi-square test to determine the frequency of the angiotensin-converting enzyme genotype and alleles and to determine the association between gene polymorphisms and normal and pathological angiograms. The chi-square test

was also used to compare the proportions of classic cardiovascular risk factors between the groups. An unpaired *t*-test was used to determine the differences in continuous variables between the groups at baseline. The OR of a pathological coronary angiogram was determined using dichotomized risk factors, including the DD genotype, as independent predictors. Multivariate logistic regression analysis was performed in three different settings (the whole population and for two age ranges, > 50 and 60 years). P-values < 0.05 were considered significant. All tests were two-tailed. The data were analyzed using SPSS version 23 (SPSS, Chicago Illinois) and G*Power version 3.1.9.7 (Heinrich Heine University, Düsseldorf, Germany).

Results

Ninety-five patients were excluded due to previous bypass surgery or angioplasty, and another 129 were excluded because they were non-menopausal at enrolment. As a result, 356 patients were included in the study (Figure 1). The mean age of those in the pathological groups was significantly older but they had lower BMI values (Table 1). In both groups, non-significant associations were found between a pathological angiogram and hypertension, dyslipidemia, smoking, a family history of CAD, and the DD genotype. However, a pathological angiogram was also associated with older age, diabetes, and BMI (Table 1).

Frequency of alleles and genotypes

The relative frequencies of II, ID, and DD genotypes were 21.3%, 50.4%, and 28.3%, respectively. The allele frequencies were 46.5% and 53.5% for inserted and deleted alleles, respectively. These results were consistent with the Hardy–Weinberg equilibrium.

Body mass index and DD genotype

There was a high prevalence of overweight patients (BMI > 25 kg/m^2) in this population (n = 244, 68.5%), and 61.5% had a pathological angiogram (n=150). Similarly, 64.3% of patients in the BMI ≤ 25 kg/m^2 group had a pathological angiogram, which was a non-significant difference (p = 0.611). There was a higher prevalence of the DD genotype in the pathological group (30.2%) than the normal group (21.6%), but this was also non-significant (Figure 2). However, among menopausal with with a BMI > 25 kg/m^2, DD genotype frequency was significantly higher in the pathological group (34%) than the normal group (19.1%), (Figure 3).

Postmenopausal cardiovascular disease has two changing factors regarding the DD genotype. First,

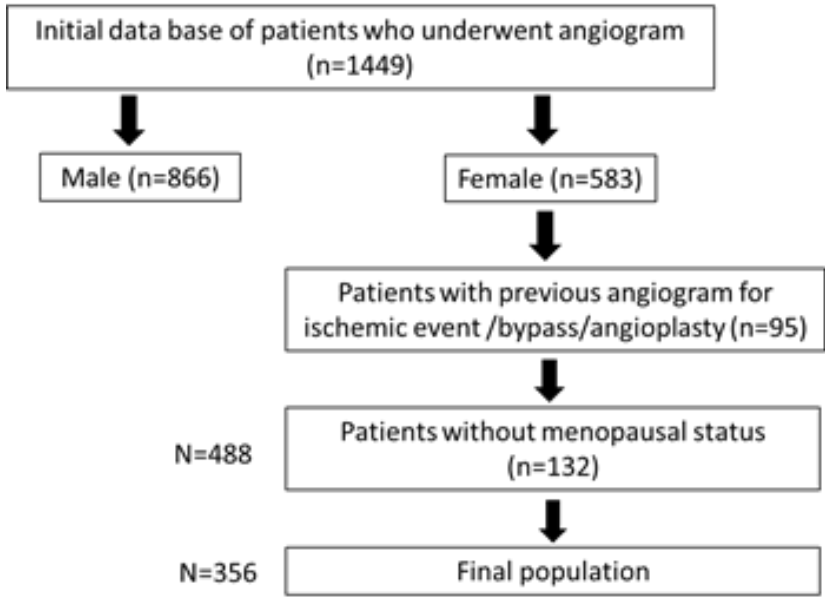


Figure 1 – Flow diagram of the study population

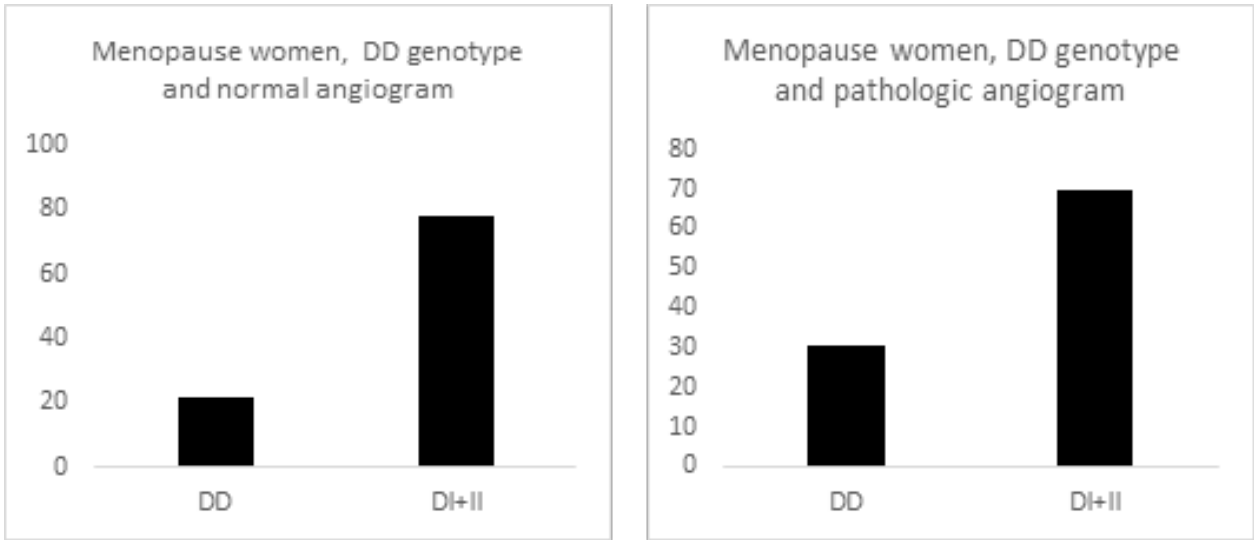


Figure 2 – DD genotype and angiogram status in menopausal women. Values expressed as percentages, p=0.079

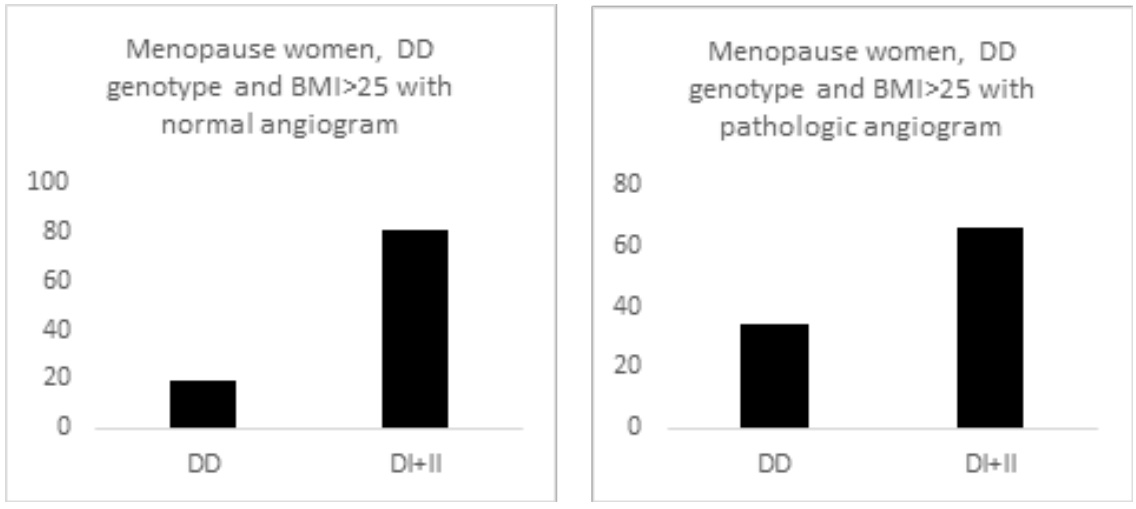


Figure 3 – DD genotype and angiogram status in menopausal women with BMI > 25. Values expressed as percentages, p=0.012

according to univariate analysis, there was an association between a pathological angiogram and age ($p < 0.001$), diabetes ($p = 0.009$), and DD genotype ($p = 0.012$) in postmenopausal women with a BMI > 25 kg/m^2. The remaining variables were not associated with pathology, although they were included in the logistic model (Table 2). In overweight women, diabetes was associated with pathology in both age ranges, but the DD genotype was only associated with the younger age range (Table 2). For women with a lower BMI, pathology was associated with age, diabetes, and hypertension. In a multivariate analysis, only age was significant ($p = 0.037$) (data not shown).

Age was significantly associated with coronary lesions in the overall population, but when divided by age, the association was not observed in the younger group (> 50 years, $p = 0.345$; > 60 years, $p = 0.057$). However, age

Table 2 – The relationship between angiogram lesion and cardiovascular risk factors in menopausal overweight women

*	B	SD	Wald	p-value	Exp(B)	95%CI	
						Inferior	Superior
M50	0.526	0.489	1.157	0.282	1.692	0.649	4.410
DM	0.666	0.288	5.358	0.021	1.946	1.107	3.418
HT	0.023	0.380	0.004	0.951	1.023	0.486	2.156
DLP	0.139	0.283	0.240	0.624	1.149	0.660	2.001
SM	-0.187	0.338	0.308	0.579	0.829	0.428	1.607
Sedentary	-0.545	0.849	0.412	0.521	0.580	0.110	3.061
DD	0.680	0.320	4.517	0.034	1.975	1.054	3.699
**	B	SD	Wald	p-value	Exp(B)	95%CI	
						Inferior	Superior
M60	0.842	0.288	8.531	0.003	2.322	1.319	4.088
DM	0.768	0.296	6.747	0.009	2.157	1.208	3.854
HT	-0.062	0.391	0.025	0.874	0.940	0.437	2.022
DLP	0.148	0.287	0.265	0.607	1.159	0.660	2.035
SM	-0.118	0.344	0.118	0.731	0.888	0.453	1.742
Sedentary	-0.702	0.877	0.641	0.423	0.496	0.089	2.762
DD	0.621	0.326	3.622	0.057	1.861	0.982	3.529

*M50: >50 years, M60: >60 years, HT: Hypertension, DM: Diabetes Mellitus, DLP: Dislipidemia, SM: Smoking. DD: presence of the DD genotype vs. II+ID, B: Beta coefficient, SD: standard deviation, Exp(B): Beta exponential, 95%CI: 95% confidence interval * and ** include tables for BMI>25 depending on age category.*

was associated with pathology in older women when evaluating the overall population. Those > 60 years had a higher risk of CAD (OR: 2.296, 95% CI: 1.296–4.068) and diabetes (OR: 2.141, 95% CI: 1.198–3.824).

There was a weak association between DD genotype and pathology in the overall population (p = 0.071), as well as in women > 60 years. However, there was a significant association between DD genotype and pathology in younger overweight patients. According to the regression analysis, there was a significant association between pathology, BMI < 25, and age (p = 0.037) but not for the remaining variables, including the DD genotype and diabetes (data not shown).

In a complementary analysis in which the traditional cutoff value of 50% luminal obstruction was used to define a pathological angiogram, the prevalence was 68.6%. Regression analysis revealed a significant association between diabetes and vessel obstruction in overweight women (p = 0.002 for > 50 years and p = 0.001 for > 60 years), but there were no significant associations with any of the other variables, including the DD genotype (data not shown).

Discussion

The pathways by which estrogen interacts with the cardiovascular system are not fully understood. Some experimental data on gene expression indicate that 17-B estradiol causes the downregulation of AT1 receptor mRNA.[21] Other studies report that estrogen interferes with neointima formation, attenuating AT1 receptor-mediated activation of extracellular signal-regulated kinases and c-fos expression, thereby inhibiting vascular smooth muscle cell proliferation, an important step in atherosclerosis.[22]

Hypothetically, the more activated renin–angiotensin system in the DD genotype could be minimized with adequate estrogen levels until a follicular age-dependent deficit is observed. At that time, hormone-associated metabolic changes in the lipid profile promote the deposition of cholesterol, and there is a greater availability of low-density lipoprotein particles associated with angiotensin II throughout the LOX-1 receptor.[23] Furthermore, in women on hormone replacement therapy, it has been shown that estrogen has lower levels of monocyte chemoattractant protein-1, which is involved in the progression of atherosclerosis by increasing both the number of macrophages and oxidized lipid accumulation in vessel walls. Other factors could also contribute to the risk of postmenopausal cardiovascular disease, one of which is obesity. In the current COVID-19 pandemic, the treatment and prevention of cardiovascular disease is receiving much attention, principally because it involves pathways that contribute to atherosclerosis.[24] Obesity has also been associated with the polymorphism of angiotensin, and ethnic differences might affect this association. In a meta-analysis of 14 studies, the DD genotype was a risk factor for obesity.[25] Differences were found between the DD and DI + II genotypes, at least among Africans, although three populations were evaluated (Asians, Caucasians, and Africans).

As expected, the authors of the review found an association between classic risk factors, hypertension, and diabetes in the univariate and multivariate analyses. In our multivariate analysis, the independent variables were age and diabetes; the latter was maintained in the three models only among patients with BMI > 25 kg/m^2.

Certain factors must be considered when determining atherosclerosis with a coronary angiogram. Mild luminal irregularities in angiography are associated with a higher disease burden and greater high-risk plaque density than when more accurate methods, such as intravascular ultrasound, are used.[26] Furthermore, nonobstructive coronary artery disease is becoming more common in women, and its risk of major adverse events is similar to obstructive CAD.[27] Thus, studying patients with obstructive lesions as well as those with lesser plaque obstruction is justifiable. Considering the disease as a continuum, it was important to compare patients with some degree of atherosclerotic lesion who required clinical or noninvasive assessment to diagnose coronary ischemia and to use a lower limit than the routine threshold of 50% in traditional angiography.[28] Moreover, through vascular remodeling, plaque can frequently modulate the vascular bed without reducing vessel volume.[29] Thus, atherosclerotic plaque could be underestimated in a routine coronary angiogram, and using the standard threshold of 50% could complicate the prediction of clinical outcomes.

Finally, apart from the expressive association between diabetes and CAD,[30] the incidence of postmenopausal cardiovascular disease appears to be strongly associated with two independent factors when evaluating the DD genotype: younger age (> 50 years) at first ischemic event, followed by weight (BMI > 25 kg/m^2). Both of these results should be explored in the angiotensin system in future studies.

Study limitations

Since this was a cross-sectional study, future outcomes, such as new coronary events (myocardial infarction or stable/unstable angina), cannot be predicted. Additionally the sample could have been larger if routine DNA testing had been performed for every patient who required a coronary angiogram for their first coronary event, which might be possible in other institutions around the world.

Potential clinical value

It is anticipated that genetic information will become increasingly available for postmenopausal patients. It is important to identify examples in which the evidence is sufficiently robust and predictive to allow genetic information to guide clinical decisions and formulate preventive guidelines for CAD.

Conclusion

These data support an association between atherosclerosis and the renin–angiotensin system in a hypoestrogenic environment, which is intensified in overweight women. This association is dependent on the age at which the ischemic event is diagnosed.

Author contributions

Conception and design of the research: Lanz-Luces JR, Costa FA. Acquisition of data: Lanz-Luces JR, Lanz-Souquett JD. Analysis and interpretation of the data: Costa FA, Guzman L, Lanz-Luces JA, Costa LA. Statistical analysis: Costa FA, Lanz-Souquett JD. Obtaining financing: Lanz-Luces JR. Writing of the manuscript:

Lanz-Luces JR, Guzman L, Lanz-Luces JA, Lanz-Souquett JD. Critical revision of the manuscript for intellectual content: Costa FA, Guzman L, Lanz-Luces JA, Costa LA.

Potential Conflict of Interest

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

Sources of Funding

This study was partially supported by grants from the *Fundação de Amparo à Pesquisa do Estado de São Paulo* (FAPESP 01-00009-0) and was partially supported by a fellowship from the SBC/FUNCOR (*Fundação do Coração*) *Fundo de Aperfeiçoamento e Pesquisa em Cardiologia.*

Study Association

This article is part of post-hoc analysis of data from a late doctoral study (2005) submitted by José Ramón Lanz Luces, from *Instituto do Coração (InCor), Escola de Medicina da Universidade de São Paulo*, São Paulo, Brazil.

References

1. Akahoshi M, Soda M, Nakashima E, Tsuruta M, Ichimaru S, Seto S, et al. Effects of age at menopause on serum cholesterol, body mass index, and blood pressure. Atherosclerosis. 2001;156(1):157-63. doi: 10.1016/s0021-9150(00)00609-2.
2. Campos H, Walsh BW, Judge H, Sacks FM. Effect of estrogen on very low density lipoprotein and low density lipoprotein subclass metabolism in postmenopausal women. J Clin Endocrinol Metab. 1997;82(12):3955-63. doi: 10.1210/jcem.82.12.4437.
3. Herrington DM, Howard TD, Hawkins GA, Reboussin DM, Xu J, Zheng SL, et al. Estrogen-receptor polymorphisms and effects of estrogen replacement on high-density lipoprotein cholesterol in women with coronary disease. N Engl J Med. 2002;346(13):967-74. doi: 10.1056/NEJMoa012952.
4. Walsh BW, Li H, Sacks FM. Effects of postmenopausal hormone replacement with oral and transdermal estrogen on high density lipoprotein metabolism. J Lipid Res. 1994;35(11):2083-93.
5. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. JAMA. 2002;288(3):321-33. doi: 10.1001/jama.288.3.321.
6. Siemińska L, Cichoń-Lenart A, Kajdaniuk D, Kos-Kudła B, Marek B, Lenart J, et al. Hormony płciowe i adipocytokiny u kobiet po menopauzie Sex hormones and adipocytokines in postmenopausal women. Pol Merkur Lekarski. 2006;20(120):727-30.
7. Cao H. Adipocytokines in obesity and metabolic disease. J Endocrinol. 2014;220(2):47-59. doi: 10.1530/JOE-13-0339.
8. Clasen R, Schupp M, Foryst-Ludwig A, Sprang C, Clemenz M, Krikov M, et al. PPARgamma-activating angiotensin type-1 receptor blockers induce adiponectin. Hypertension. 2005;46(1):137-43. doi: 10.1161/01.HYP.0000168046.19884.6a.
9. Berg AH, Combs TP, Scherer PE. ACRP30/adiponectin: an adipokine regulating glucose and lipid metabolism. Trends Endocrinol Metab. 2002;13(2):84-9. doi: 10.1016/s1043-2760(01)00524-0.
10. Tzoulaki I, Murray GD, Lee AJ, Rumley A, Lowe GD, Fowkes FG. C-reactive protein, interleukin-6, and soluble adhesion molecules as predictors of progressive peripheral atherosclerosis in the general population: Edinburgh Artery Study. Circulation. 2005;112(7):976-83. doi: 10.1161/CIRCULATIONAHA.104.513085.
11. Guo F, Chen XL, Wang F, Liang X, Sun YX, Wang YJ. Role of angiotensin II type 1 receptor in angiotensin II-induced cytokine production in macrophages. J Interferon Cytokine Res. 2011;31(4):351-61. doi: 10.1089/jir.2010.0073.
12. Niu T, Chen X, Xu X. Angiotensin converting enzyme gene insertion/deletion polymorphism and cardiovascular disease: therapeutic implications. Drugs. 2002;62(7):977-93. doi: 10.2165/00003495-200262070-00001.
13. Méthot J, Hamelin BA, Arsenault M, Bogaty P, Plante S, Poirier P. The ACE-DD genotype is associated with endothelial dysfunction in postmenopausal women. Menopause. 2006;13(6):959-66. doi: 10.1097/01.gme.0000243576.09065.93.
14. Amara A, Mrad M, Sayeh A, Lahideb D, Layouni S, Haggui A, et al. The Effect of ACE I/D Polymorphisms Alone and With Concomitant Risk Factors on Coronary Artery Disease. Clin Appl Thromb Hemost. 2018;24(1):157-163. doi: 10.1177/1076029616679505.
15. Gardemann A, Fink M, Stricker J, Nguyen QD, Humme J, Katz N, et al. ACE I/D gene polymorphism: presence of the ACE D allele increases the risk of coronary artery disease in younger individuals. Atherosclerosis. 1998;139(1):153-9. doi: 10.1016/s0021-9150(98)00040-9.
16. Pardhe BD, Ghimire S, Shakya J, Pathak S, Shakya S, Bhetwal A, et al. Elevated Cardiovascular Risks among Postmenopausal Women: A Community Based Case Control Study from Nepal. Biochem Res Int. 2017;2017:3824903. doi: 10.1155/2017/3824903.
17. Collins KMT, Onwuegbuzie AJ, Jiao QG. A mixed methods investigation of mixed methods sampling designs in social and health science research. Journal of Mixed Methods Research 2007;1(3):267-294. doi: 10.1177/1558689807299526.
18. Lanz JR, Pereira AC, Lemos PA, Martinez E, Krieger JE. Angiotensinogen M235T polymorphism is associated with coronary artery disease severity. Clin Chim Acta. 2005;362(1-2):176-81. doi: 10.1016/j.cccn.2005.06.004.
19. Nallamothu BK, Spertus JA, Lansky AJ, Cohen DJ, Jones PG, Kureshi F, et al. Comparison of clinical interpretation with visual assessment and quantitative coronary angiography in patients undergoing percutaneous coronary intervention in contemporary practice: the Assessing Angiography (A2) project. Circulation. 2013;127(17):1793-800. doi: 10.1161/CIRCULATIONAHA.113.001952.
20. Morabia A, Costanza MC. International variability in ages at menarche, first livebirth, and menopause. World Health Organization Collaborative Study of Neoplasia and Steroid Contraceptives. Am J Epidemiol. 1998;148(12):1195-205. doi: 10.1093/oxfordjournals.aje.a009609.
21. Nickenig G, Strehlow K, Wassmann S, Bäumer AT, Albory K, Sauer H, et al. Differential effects of estrogen and progesterone on AT(1) receptor gene expression in vascular smooth muscle cells. Circulation. 2000;102(15):1828-33. doi: 10.1161/01.cir.102.15.1828.
22. Liu HW, Iwai M, Takeda-Matsubara Y, Wu L, Li JM, Okumura M, et al. Effect of estrogen and AT1 receptor blocker on neointima formation. Hypertension. 2002;40(4):451-7. doi: 10.1161/01.hyp.0000033466.05496.89.
23. Pirillo A, Norata GD, Catapano AL. LOX-1, OxLDL, and atherosclerosis. Mediators Inflamm. 2013;2013:152786. doi: 10.1155/2013/152786.
24. Zhu Y, Xian X, Wang Z, Bi Y, Chen Q, Han X, et al. Research Progress on the Relationship between Atherosclerosis and Inflammation. Biomolecules. 2018;8(3):80. doi: 10.3390/biom8030080.

25. Mao S, Huang S. A meta-analysis of the association between angiotensin-converting enzyme insertion/ deletion gene polymorphism and the risk of overweight/obesity. J Renin Angiotensin Aldosterone Syst. 2015;16(3):687-94. doi: 10.1177/1470320313501218.

26. Briguori C, Tobis J, Nishida T, Vaghetti M, Albiero R, Di Mario C, et al. Discrepancy between angiography and intravascular ultrasound when analysing small coronary arteries. Eur Heart J. 2002;23(3):247-54. doi: 10.1053/euhj.2001.2730.

27. Pepine CJ, Ferdinand KC, Shaw LJ, Light-McGroary KA, Shah RU, Gulati M, et al. Emergence of Nonobstructive Coronary Artery Disease: A Woman's Problem and Need for Change in Definition on Angiography. J Am Coll Cardiol. 2015;66(17):1918-33. doi: 10.1016/j.jacc.2015.08.876.

28. Rumberger JA. Coronary Artery Disease: A Continuum, Not a Threshold. Mayo Clin Proc. 2017;92(3):323-326. doi: 10.1016/j.mayocp.2017.01.009.

29. Birnbaum Y, Fishbein MC, Luo H, Nishioka T, Siegel RJ. Regional remodeling of atherosclerotic arteries: a major determinant of clinical manifestations of disease. J Am Coll Cardiol. 1997;30(5):1149-64. doi: 10.1016/s0735-1097(97)00320-3.

30. Naito R, Miyauchi K. Coronary Artery Disease and Type 2 Diabetes Mellitus. Int Heart J. 2017;58(4):475-480. doi: 10.1536/ihj.17-191.

Int J Cardiovasc Sci. 2021; 34(4):420-430

ORIGINAL ARTICLE

Metabolic Syndrome and Risk of Cardiovascular Diseases in Female Breast Cancer Survivors

Leandro Marques da Silva and José Albuquerque de Figueiredo Neto

Universidade Federal do Maranhão, São Luís, MA – Brazil

Abstract

Background: The implementation of intensive therapy protocols increases the probability of adverse events in patients with breast cancer (BC). Components of metabolic syndrome (MS) are among these events.

Objective: To verify the prevalence of MS and cardiovascular disease (CVD) risk in female BC survivors.

Materials and Methods: This is a descriptive, observational, cross-sectional study. Our sample comprised 60 women without BC (G1) and 60 women who had survived BC (G2). We collected sociodemographic, anthropometric, tumor, and clinical data. After variable analysis, the participants received positive or negative MS diagnoses and a 10-year CVD risk stratification. The significance level adopted for the analyses was 5% ($p < 0.05$) and the confidence interval (CI) was 95%. For comparing categorical data, we used the chi-squared, Fisher's exact, or G tests; for comparing continuous data, we used the parametric Student's t-test and the non-parametric Mann-Whitney test.

Results: Both groups presented overweight and an increased waist-to-hip ratio. Weight, body mass index, abdominal circumference, hip circumference, and low-density cholesterol were variables that presented statistically significant differences between groups. MS was diagnosed in 32% of women in G1 and 45% of those in G2. Regarding the 10-year risk for CVD, most women were in the low-risk stratum: the mean total risk of CVD occurrences was 7.48% in G1 and 7.70% in G2.

Conclusion: We observed a higher prevalence of MS among women who survived BC, possibly due to overweight, as well as a low 10-year risk for CVD after cancer treatment. Although we did not observe a statistically significant difference, we suggest the adoption of a healthy lifestyle and rigorous control of cardiometabolic risk factors.

Keywords: Metabolic Syndrome; Heart Diseases; Breast Neoplasms.

Introduction

Cancer represents the second main cause of death worldwide, behind only cardiovascular diseases (CVD).[1] Projections for 2030 expect around 24 million cases of cancer and 14.6 million deaths.[2] This disease represents a global health challenge that has been increasing in low-and middle-income countries with the globalization of the economy and lifestyles.[3] Among various neoplasm types, breast cancer (BC) is the one that affects women the most each year, being responsible for 23% (1 380 000) of all new cancer cases and 14% (458 400) of all deaths due to cancer.[4]

The number of long-term cancer survivors is increasing. A better organization of cancer care, more effective treatment options, and evidence-based tumor-specific protocols are factors that have contributed to this increase.[5-7] However, 2 out of 3 cancer survivors are prone to suffering from complications in the long term.[8] A wide spectrum of late adverse effects such as CVD, diabetes, dyslipidemia, arterial hypertension, osteoporosis, and metabolic syndrome (MS) components are likely to develop among cancer survivors. For this reason, it is important to design appropriate health management strategies for these patients.[7,9-10]

Leandro Marques da Silva, Me.
Health Research and Development Coordinator
Escola de Saúde Pública do Estado do Maranhão - ESP/MA

Mailing Address: Leandro Silva
Av. dos Portugueses, 1966. Postal Code: 65085-580, Vila Bacanga, São Luís, MA – Brazil.
E-mail: leandromks16@hotmail.com, jafneto@terra.com.br

DOI: https://doi.org/10.36660/ijcs.20200411

Manuscript received October 02, 2020; revised manuscript November 23, 2020; accepted April 26, 2021.

Studies show a high prevalence of MS in the Brazilian population. One of these population studies found a MS prevalence of 29.8% in adults (95% confidence interval [CI]).[4] In a study performed with 50 women with BC aged between 40 and 80 years and 50 age-matched controls, the prevalence of MS was 40.0% among patients with BC and 18.0% in the control group (P = 0.02). A positive independent association was observed between MS and risk of BC (odds ratio [OR] = 3.037; 95% CI 1.214–7.597).[11]

In MS, adipocytes and adipokines derived from the perivascular adipose tissue such as leptin, resistin, IL-6, and tumor necrosis factor-α are potent pro-inflammatory molecules that may promote oxidative stress in the endothelium and affect endothelial function,[12] leading to a predisposition to CVD.[13,14] In this context, a new subspecialty has emerged within the cardiology field: cardio-oncology, where cardiologists participate in a multidisciplinary team dedicated to cancer treatment. Before initiating treatment, it is important to identify patients at increased risk for cardiac toxicity so that alternative, less cardiotoxic treatment options can be considered.[15,16]

The aim of the present study was to verify the prevalence of MS and CVD risk in female BC survivors (BCS).

Materials and Methods

Study Type and Site

This research was characterized as a descriptive, observational, cross-sectional study. Sample selection occurred at a philanthropic hospital located in São Luís, state of Maranhão (MA), which is a high-complexity oncology referral center.

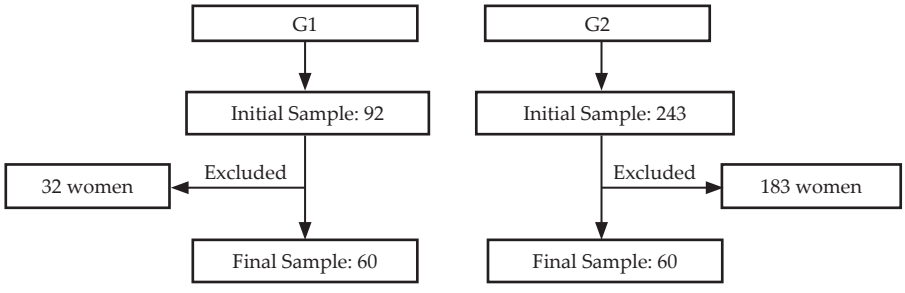
Ethical Aspects

This study was based on ethical principles that rule research with human beings and followed Resolution No. 466/12 of the National Health Council. The project was approved by the Ethics and Research Committee (CEP) of *Universidade Federal do Maranhão* according to opinion No. 2 386 296. Participants signed a free and informed consent form (FICF) and received information on the main aspects of the study such as the procedure, objective, and possible contributions; they were free to withdraw their participation at any moment of the study and at no penalty or charge.

Sample

The sample consisted of 120 female patients and was divided into 2 groups: G1, 60 women with no BC diagnosis, and G2, 60 female BCS (Flow Diagram 1). These corresponded to the required sample size according to previous sample size calculations which used the formula for the proportion of 2 samples, since we aimed to investigate data on the prevalence of MS in 2 distinct groups, for comparison purposes. The study used as reference for this calculation was performed by Ortiz et al. (2014).[17]

Out of a sample of 92 women selected from the general population, after applying inclusion and exclusion criteria, we obtained a selection of 60 women for the G1 group. Meanwhile, out of 243 women with BC (G2), we selected 60 women according to the selected inclusion and exclusion criteria. The selection of participants for G2 was performed by the recruitment of patients registered at the Hospital Cancer Registry (HCR) of the aforementioned hospital.



Flow Diagram 1 – The study's patient selection process.

Inclusion and Exclusion Criteria

We selected women aged between 35 and 60 years for this study. In G1, BC-free women as per medical confirmations performed in the previous 2 months. In G2, female BCS according to a medical certificate, with staging levels I, II, or III, positive pathology examination of the sentinel lymph node, who were treated at the study hospital and who accepted to participate in the study by signing the FICF. BCS who had had a complete axillary dissection were excluded from the study. We also excluded, from both groups, patients who were pregnant or who had ascites due to the difficulty in identifying abdominal obesity; patients who had any type of heart disease of any etiology, according to their clinical history and physical examination; those who had a clinical manifestation of atherosclerosis or genetically proven dyslipidemias; those who had infectious diseases or kidney and/or liver diseases; patients who presented physical, psychic, cognitive, and sensorial alterations that prevented the execution of the study tests; and those who refused to participate in any of the study's stages.

Data Collection

The study began after the selected patients received information regarding the ethical aspects of the research and signed the FICF, as determined by Resolution No. 466/12 of the National Bioethics Commission of Brazil (CONEP). We collected sociodemographic data, as well as information on date of diagnosis, staging level, treatment modalities, and other data from the HCR.

Participants selected for both groups were then invited to the Clinical Research Center of Hospital Universitário da Universidade Federal do Maranhão (CEPEC- HUUFMA), where blood collections and other measurements were performed. Initially, we requested a 12-hour fast before blood collection; then, women answered questionnaires on their age, sociodemographic information, the occurrence of other comorbidities or menopause, use of medications, and smoking and drinking habits.

For obtaining arterial pressure (AP) values, patients were seated, with feet on the ground, and the measurement was performed after 5 minutes of rest. Measurements were performed using the non-operated arm (as was the blood collection). We performed 3 consecutive readings for each participant, with a 3-minute interval. The first reading was discarded, and the mean value between the 2 other measurements was used. We also investigated weight (kg) using an electronic scale and height (m) with a wall-mounted stadiometer, as well as abdominal circumference/waist (AC) and hip circumference (HC) with a tape measure, which allowed us to determine the waist-to-hip ratio (WHR). The body mass index (BMI) was calculated by dividing weight (in kg) by height (in m) squared.

Subsequently, blood collection was performed at the hospital's laboratory. The biochemical investigation included total cholesterol and triglycerides (TG) measured by the endpoint colorimetric method and high-density lipoprotein (HDL-cholesterol) measured by the selective precipitation method coupled with the endpoint colorimetric method. Low-density lipoprotein (LDL-cholesterol) and very low-density lipoprotein (VLDL) were obtained through the Friedewald formula: LDL cholesterol (mg/dL) = total cholesterol - HDL-cholesterol - (triglycerides/5); this formula was valid for TG values of up to 400 mg/dL.

Glycemia, in turn, was quantified by the glucose oxidase enzymatic method. Serum insulin concentrations were also determined. Insulin resistance diagnoses were established according to the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) index, which is the product of fasting insulin (mUI/mL) and fasting glycemia (mmol/L) divided by 22.5. Insulin resistance was defined when values were higher than 3.16. After analyzing all collected data, participants received a positive or negative MS diagnosis.

MS diagnoses were established according to criteria by the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III), being positive when 3 or more of the following parameters were present: 1) abdominal fat: an AC of more than 88 cm; 2) low HDL-cholesterol levels (less than 50 mg/dL); 3) elevated TG levels (150 mg/dL or more); 4) elevated AP (135/85 mmHg or more); 5) elevated glycemic levels (110 mg/dL or more). For analyzing cardiovascular risk, we used the Framingham risk score.

According to this score, each variable has value ranges with specific positive or negative scores. The total score considers the following variables: sex, age, smoking habits, diabetes mellitus, HDL-cholesterol, total cholesterol, systolic arterial pressure, and diastolic arterial pressure. The final score corresponds to the possibility (in %) of occurrence of a cardiovascular disease in the next 10 years. Therefore, individuals are classified into the following categories: low risk (with a 10-year cardiovascular risk of less than 10%), intermediate risk (between 10% and 20%), and high risk (more than 20%).

Data Analyses

The collected data were stored and analyzed using SPSS, version 2. The significance level adopted for our analyses was 5% ($p < 0.05$) and a 95% CI. Continuous variables with normal distribution were described as means ± standard deviations, and those that did not present normal distributions were described as median values and interquartile ranges. Firstly, the Kolmogorov-Smirnov test was applied for testing the hypothesis that data followed a normal distribution and helping in the choice between parametric and non-parametric tests through which the significance of data between groups was verified. Therefore, for comparing categorical data we used the chi-squared, Fisher's exact, or G tests, and for comparing continuous data we used the parametric independent samples Student's t-test and the non-parametric Mann-Whitney test.

We used logistic regression models for estimating OR and 95% CI and verifying which variables influenced the occurrence of MS in female BCS. The models included an isolated analysis of variables that presented a statistically significant difference when compared with the control group regarding MS.

Results

Mixed-race participants and those with secondary education were the most prevalent in both groups. Considering family income, we observed that participants of this study had a low socioeconomic status, since 40% of the control group had a family income of ½ to 1 minimum wage and the same percentage earned 1 to 2 times the minimum wage in the BCS group. Most women reported not practicing regular physical exercise or having a family history of cancer, as well as not smoking or drinking; this last variable presented a statistical difference from the control group, as did the presence of menopause (Table 1).

Regarding the characteristics of tumors and the performed treatment (Table 2), the right breast had been affected in 60% of female BCS. Considering staging levels, the most prevalent was stage II (43.3%). As for treatment, 86.6% underwent a complete protocol (surgery, chemotherapy, and radiotherapy), with varying orders according to clinical characteristics and the tumor's anatomopathological aspects. The mean follow-up time, representing the end of treatment and follow-up, was 4 years.

When comparing anthropometric parameters and metabolic risk factors among female BCS and the control group (Table 3), we observed that both groups presented overweight (mean BMI of 26.08 kg/m^2 in the control group and 29.27 kg/m^2 in the female BCS group). The WHR in both groups was over 0.86, which is the threshold for identifying high cardiovascular risk. Cholesterol levels were above normal values for women, with mean values of 200.46 mg/dL and 213.98 mg/dL in the control and BCS groups, respectively. Some variables presented statistically significant differences between groups, such as weight, BMI, AC, HC, and LDL-cholesterol.

Variables that presented statistically significant differences between groups were analyzed by a logistic regression model. Through this model, we identified that isolated variables did not increase the OR for MS, except for HC (Table 4).

The identification of MS in both groups, according to NCEP-ATP III criteria, is demonstrated in Graph 1. In this graph, we observe a higher occurrence of MS in the BCS group, with 27 women (45%), in contrast to 19 (32%) in the control group. When comparing groups, we did not observe a statistically significant difference.

In the 10-year CVD risk stratification according to Framingham scores (Table 5), we obtained a high prevalence of low cardiovascular risk in both groups (73% in the control group and 72% in female BCS), with no statistically significant differences between groups according to Student's t- and Mann-Whitney testing of the obtained scores.

For assessing the mean cardiovascular risk in both groups (Graph 2), we obtained a 10-year risk for developing CVD of 7.48% in the control group and 7.70% among female BCS. When comparing groups, we did not observe a statistically significant difference ($p > 0.05$).

Discussion

Women in both groups presented similar socioeconomic and clinical characteristics, such as low schooling levels and low socioeconomic status (Table 1). These factors influence the level of knowledge on diseases in general and the adoption of healthy lifestyles,[5] which could explain the low prevalence of regular physical activity among women in this study. This fact directly impacts MS and CVD risk factors.[1] However, female BCS had less damaging life habits, such as lower levels of smoking and drinking, when compared to the control

Table 1 – Socioeconomic and clinical characteristics of female breast cancer survivors and the control group. São Luís-MA, 2021

Characteristics	Control group (n = 60)	BCS group (n = 60)	*p*
Race			
White	10 (17%)	10 (17%)	
Black	16 (27%)	19 (32%)	0.849[b]
Mixed-race	33 (55%)	29 (48%)	
Asian	1 (2%)	2 (3%)	
Schooling			
Incomplete primary/lower secondary education	8 (13%)	3 (5%)	
Primary/lower secondary education	5 (8%)	4 (7%)	
Incomplete secondary education	5 (8%)	6 (10%)	0.543[b]
Secondary education	33 (55%)	34 (57%)	
Incomplete tertiary education	3 (5%)	2 (3%)	
Tertiary education	6 (10%)	11 (18%)	
Family income			
< ½ MW	3 (5%)	6 (10%)	
½ to 1 MW	24 (40%)	14 (23%)	
1 to 2 MW	22 (37%)	24 (40%)	0.222[b]
2 to 5 MW	10 (17%)	16 (27%)	
> 5 MW	1 (2%)	0 (0%)	
Physical activity			
Yes	47 (78%)	42 (70%)	0.297[a]
No	13 (22%)	18 (30%)	
FH of cancer			
No	40 (67%)	36 (60%)	0.448[a]
Yes	20 (33%)	24 (40%)	
Menopause			
No	29 (48%)	9 (15%)	**<0.0001[a]**
Yes	31 (52%)	51 (85%)	
Smoking			
No	55 (92%)	58 (97%)	0.439[c]
Yes	5 (8%)	2 (3%)	
Drinking			
No	38 (63%)	56 (93%)	**0.0001[c]**
Yes	22 (37%)	4 (7%)	

BCS: breast cancer survivors; MW: times the minimum wage; FH: family history; a: chi-squared test; b: G test; c: Fisher's exact test.

Table 2 – Characteristics of tumors and treatments underwent by the female breast cancer survivor group. São Luís- MA, 2021

Characteristics	n	%
Tumor location		
Right breast	36	60.0
Left breast	24	40.0
Staging		
I	11	18.3
II	26	43.3
III	23	38.3
Treatment		
C + S + R	21	35.0
C + S + R	25	41.6
C + R + S	5	8.3
C + R + S	1	1.7
C + S	5	8.3
C + R	1	1.7
C + S	1	1.7
S	1	1.7
Follow-up time (years)	4 ± 2.44	

C: chemotherapy, S: surgery, R: radiotherapy

group. The higher prevalence of menopause among BCS may be related to chemotherapy treatment, which favors its early development.[7]

The anthropometric parameters and metabolic risk factors directly related to obesity (weight, BMI, AC, HC, and LDL-cholesterol) were elevated in female BCS, with statistically significant differences when considering the control group (Table 3). Results of a controlled and well-designed study with some of these variables demonstrated that cancer survivors were more dyslipidemic than the control population.[16] The increase in BMI among post-menopausal women mainly results from an associated increase in estrogens.[18] In addition, the pain, fatigue, and weakness associated with chemotherapy may cause physical inactivity, leading to abdominal obesity. Moreover, an unhealthy diet and lack of exercise increase visceral fat, leading to MS and chronic diseases such as obesity, hypertension, and diabetes.[19]

A prospective study performed in Denmark with women with BC revealed that those who had a BMI of 30 kg/m^2 or higher presented more advanced disease at diagnosis when compared to those who had a BMI of less than 25 kg/m.[24] Another study performed in the United States observed that, in women who gained weight after a BC diagnosis, each 5-kg gain was associated with a 13% increase in specific mortality, concluding that an elevated BMI was associated to higher mortality rates due to BC.[18] The presence of visceral adipose tissue can lead to MS due to its hyperlipolytic state and contribution of free fatty acids to the increase in insulin resistance.[16] Therefore, it is extremely important to routinely assess the nutritional status of women with BC with easily obtainable anthropometric measures such as BMI and AC.[4]

Female BCS face approximately twice the risk of death due to CVD and other chronic diseases than age-matched

Table 3 – Comparison between anthropometric parameters and metabolic risk factors between female breast cancer survivors and the control group. São Luís-MA, 2021

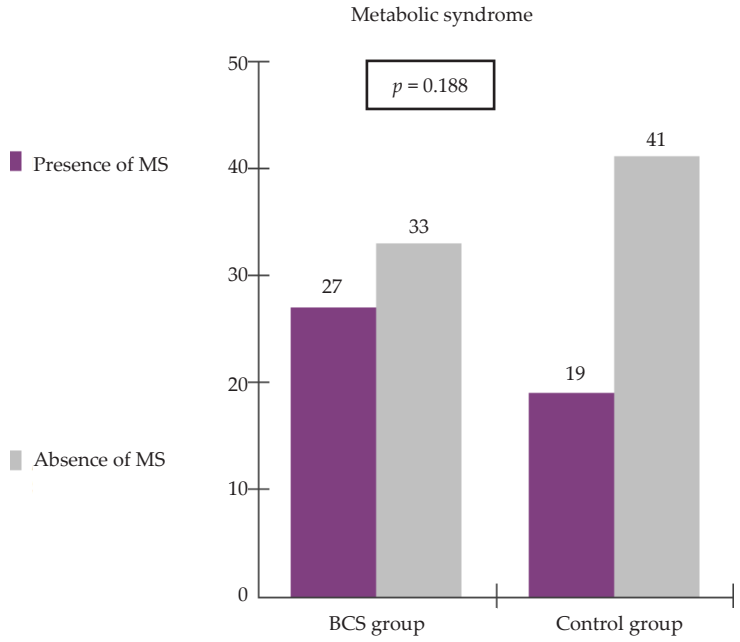
Variables	Control group (mean ± SD)	BCS group (mean ± SD)	p
Age (years)	49.06 ± 6.22	48.86 ± 7.23	0.871[a]
DAP (mmHg)	86.08 ± 14.11	83.5 ± 14.24	0.320[a]
Weight (Kg)	62.15 ± 11.45	69.36 ± 13.01	**0.002**[a]
Height (m)	1.54 ± 0.05	1.53 ± 0.05	0.703[a]
BMI (Kg/m²)	26.08 ± 4.40	29.27 ± 5.18	**0.0004**[a]
AC (cm)	86.18 ± 15.33	92.08 ± 13.56	**0.021**[a]
HC (cm)	93.63 ± 9.33	99.89 ± 11.49	**0.001**[a]
HDL (mg/dL)	49.73 ± 14.9	49.43 ± 13.02	0.907[a]
LDL (mg/dL)	118.87 ± 35.54	132.5 ± 30.20	**0.020**[a]
VLDL (mg/dL)	32.10 ± 12.53	28.86 ± 10.90	0.134[a]
Triglycerides (mg/dL)	159.83 ± 59.07	143.25 ± 61.98	0.136[a]
	Median / IQR (25–75)	**Median / IQR (25–75)**	
SAP (mmHg)	120 110–132.5	120 110–130	0.636[b]
Cholesterol (mg/dL)	202 181–238.3	197.5 178.5–221.5	0.271[b]
WHR	0.92 0.84–0.95	0.93 0.89–0.97	0.207[b]
Glycemia (mg/dL)	95.5 89–104.5	90.5 85–102.25	0.096[b]
Insulin (μUI/mL)	5.79 3.50–12.3	6.81 3.40–1.03	0.603[b]
HOMAR- IR	1.42 0.84–2.93	1.65 0.74–2.71	0.437[b]

SD: standard deviation; IQR: interquartile range; BCS: breast cancer survivors; SAP: systolic arterial pressure; DAP: diastolic arterial pressure; BMI: body mass index; AC: abdominal circumference; HC: hip circumference; WHR: waist:to-hip ratio; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein; HOMAR-IR: Homeostasis Model Assessment for Insulin Resistance; a: Student's t-test; b: Mann-Whitney test. p < 0.05 (significance).

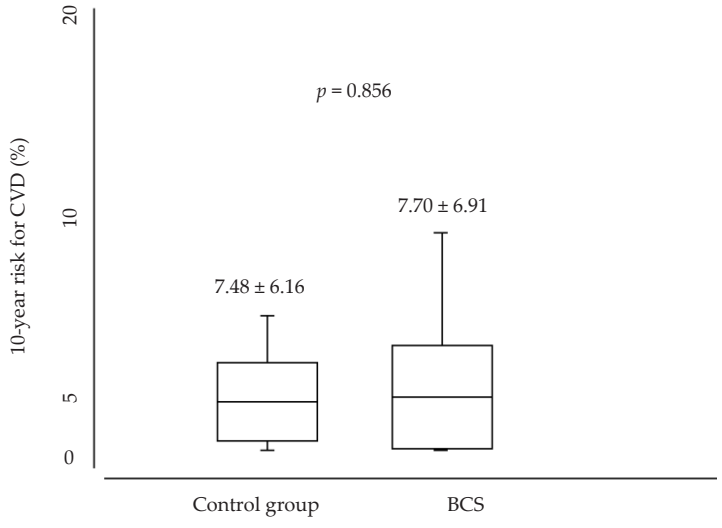
women with no cancer history.[20] In this study, we observed that almost half of our sample (45%) of BCS were diagnosed with MS. Similar results were observed in another study, where MS was present in 50% of female BCS and in 37.5% of participants in the control group. In this study, the most frequently observed diagnostic criteria were abdominal obesity (62.5%) and dyslipidemia (45.2%).[10] Another study, also performed with women with BC, reported that 69.2% of post-menopausal women had MS and 53.8% had advanced cancer stages, demonstrating that MS could influence a worsening of the BC prognosis.[4]

In a prospective study with 2092 patients followed-up due to BC, MS was significantly associated with menopause, HOMA-IR index, HC, and hypertension.[21] This corroborates findings from this study, where our logistic regression (Table 4) identified a higher risk of developing MS in women with increased HC. The occurrence of MS is 2.2 to 4.4 times higher in BCS than in the general population. These findings may reflect a lack of interest and education on MS among BCS.[5]

Drugs commonly used in cancer treatments, such as anthracyclines, camptothecins, epipodophyllotoxins, and platin-based agents, interrupt DNA replication and protein transcription and synthesis, thus compromising cell regeneration and growth. These agents may interact with receptors or second messengers, inducing gonadal hormone deficiencies, and produce reactive oxygen species leading to mitochondrial dysfunction. Anemia, apoptosis, and cell lysis may lead to tissue hypoxia, causing the liberation of pro-inflammatory cytokines and macrophage activation. All these effects



Graph 1 – Comparative analysis of metabolic syndrome (MS) diagnoses between female breast cancer survivors (BCS) and the control group, according to the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) criteria. Chi-squared test.



Graph 2 – Mean total 10-year risk for cardiovascular disease (CVD) in female breast cancer survivors (BCS) and the control group, according to the Framingham score. Student's t-test.

Table 4 – Impact of variables in the development of metabolic syndrome in female breast cancer survivors, after logistic regression. São Luís-MA, 2021

Variables	p	OR	(95% CI)
Menopause	0.630	0.684	0.15 to 3.12
Weight (Kg)	0.598	1.037	0.91 to 1.19
BMI (Kg/m²)	0.658	0.918	0.63 to 1.34
AC (cm)	0.455	1.056	0.91 to 1.22
HC (cm)	0.028	0.000	0.00 to 0.13
LDL (mg/dL)	0.853	0.998	0.98 to 1.20

OR: odds ratio; CI: confidence interval; BMI: body mass index; AC: abdominal circumference; HC: hip circumference; WHR: waist-to-hip ratio; LDL: low-density lipoprotein.

Table 5 – Risk of cardiovascular diseases in female breast cancer survivors (BCS) and the control group, according to the Framingham score. São Luís-MA, 2021

Cardiovascular risk	Control group		BCS group		*p*
	n	mean risk	n	mean risk	
Low	43 (73%)	4.48 %	44 (72%)	4.34 %	0.411[b]
Intermediate	15 (22%)	13.13 %	13 (25%)	14.48 %	0.750[a]
High	2 (5%)	29.50 %	3 (3%)	27.66 %	0.640[a]

A: Student's t-test; b: Mann-Whitney test. p < 0.05 (significant).
Note: the Student's t- and Mann-Whitney tests assessed differences between scores obtained in both groups in the Framingham scale (continuous variable). On table 5, such scores were transformed in percent values for risk stratification.

may contribute to the development of obesity, insulin resistance, and dyslipidemia, and ultimately to MS.[10]

Female BCS in this study had a mean Framingham risk score of 7.70%, thus being stratified as at low risk for CVD in 10 years (Graph 2). On the other hand, the WHR (which identifies the current cardiovascular risk according to an individual's body fat distribution) was above the threshold in both groups (Table 3), classifying them as at high CVD risk. Although the mean Framingham score in this study was lower than that reported by other studies, evidence shows that patients who underwent cancer treatment had a subsequent increase in CVD risk. The risk of developing CVD among patients with BC who underwent chemotherapy was 3 times higher than in patients who underwent surgery only, and it was 4.22 times higher in patients who had chemotherapy and radiotherapy.[22]

According to cardio-oncologists, cardiotoxic therapies (including chemotherapy or radiotherapy) are the main contributors to an increase in CVD risk in BCS.[23] In a case-control study with 2168 women from Northern Europe with breast adenocarcinoma treated with radiotherapy,[24] each 7 Gy of radiation corresponded to an increase in cardiovascular risk of 7.4%. The risk was observed 5 years after receiving radiotherapy and persisted for 30 years.[25] Moreover, depression, anxiety, and stress and/or anguish were associated with a 30% increase in MS prevalence among cancer survivors. Many subjacent pathophysiological associations may also be driven by psychological health. Stress involving the exposure to treatment may cause interruptions in the production of hormones and neurotransmitters, which influences cardiovascular risk.[26]

A meta-analysis of data from 289 109 patients demonstrated that mortality due to CVD was higher among women who underwent radiation therapy for BC in the left breast in comparison to those who had it in the right breast.[27] This way, our findings indicating that the right breast was more affected and a mean follow-up to the end of treatment of only 4 years (according to Table 2) may explain the low 10-year risk for CVD in female BCS and the absence of statistical differences when compared to the control group ($p > 0.05$).

Despite some limitations, such as the difficulty in establishing a causal association between the analyzed variables and MS due to the sample size and cross-sectional nature of the study, our work provided important clinical information on cardiometabolic factors present in BCS. This is the first step for identifying the frequency of risk factors in BCS, allowing the allocation of important subsidies for elaborating public health policies and personalized treatment plans that are less harmful and cardiotoxic.[28-29]

Conclusion

This study demonstrated a higher prevalence of MS among female BCS, possibly due to overweight. Although the studied population presented a low risk for CVD, we recommend that female BCS adopt healthy lifestyles, as well as rigorous screening and control of cardiometabolic risk factors. However, longitudinal cohort studies with these women are still needed for the development of more accurate risk prediction models for MS and CVD.

Author contributions

Conception and design of the research: LM Silva. Acquisition of data: LM Silva. Analysis and interpretation of the data: LM Silva. Statistical analysis: LM Silva, JA Figueiredo Neto. Writing of the manuscript: LM Silva, JA Figueiredo Neto. Critical revision of the manuscript for intellectual content: JA Figueiredo Neto.

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 Leandro Marques da Silva, from *Universidade Federal do Maranhão*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Universidade Federal do Maranhão* under the protocol number 2.386.296. 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. Park B, Kong SY, Lee EK, Lee MH, Lee ES. Metabolic syndrome in breast cancer survivors with high carbohydrate consumption: the first report in community setting. Clin Nutr. 2017;36(5):1372-7. doi: 10.1016/j.clnu.2016.09.006.
2. Sperling LS, Mechanick JI, Neeland IJ, Herrick CJ, Després JP, Ndumele CE, et al. The CardioMetabolic Health Alliance: working toward a new care model for the metabolic syndrome. J Am Coll Cardiol. 2015;66(9):1050-67. doi: 10.1016/j.jacc.2015.06.1328.
3. Bellastella G, Scappaticcio L, Esposito K, Giugliano D, Maiorino MI. Metabolic syndrome and cancer: "The common soil hypothesis". Diabetes Res Clin Pract. 2018;143:389-97. doi: 10.1016/j.diabres.2018.05.024.
4. Mialich MS, Silva BR, Cruz LAP, Almeida AM, Gozzo TO, Jordao AF. Assessment of the nutritional and metabolic profile of women with breast cancer and its association with metabolic syndrome. J Nutr Intermed Metab. 2018;12:14-19. doi: 10.1016/j.jnim.2018.05.004 2.
5. Seo Y, Kim JS, Park ES, Ryu E. Assessment of the awareness and knowledge of cancer survivors regarding the components of metabolic syndrome. PLoS One. 2018;13(6):e0199142. doi: 10.1371/journal.pone.0199142.
6. Serra MC, Goldberg AP, Ryan AS. Increased depression and metabolic risk in postmenopausal breast cancer survivors. Diabetol Metab Syndr. 2016;8:44. doi: 10.1186/s13098-016-0170-4.
7. Westerink NL, Nuver J, Lefrandt JD, Vrieling AH, Gietema JA, Walenkamp AM. Cancer treatment induced metabolic syndrome: improving outcome with lifestyle. Crit Rev Oncol Hematol. 2016;108:128-36. doi: 10.1016/j.critrevonc.2016.10.011.
8. Kero AE, Madanat-Harjuoja LM, Järvelä LS, Malila N, Matomäki J, Lähteenmäki PM. Health conditions associated with metabolic syndrome after cancer at a young age: a nationwide register-based study. Cancer Epidemiol. 2016;41:42-9. doi: 10.1016/j.canep.2016.01.009.
9. Kim MH, Huh JY, Lim DJ, Kang MI. Does the risk of metabolic syndrome increase in thyroid cancer survivors? Thyroid. 2017;27(7):936-43. doi: 10.1089/thy.2016.0624.
10. Casco S, Soto-Vega E. Development of metabolic syndrome associated to cancer therapy: review. Horm Cancer. 2016;7(5-6):289-95. doi: 10.1007/s12672-016-0274-1.

11. Wani B, Aziz SA, Ganaie MA, Mir MH. Metabolic syndrome and breast cancer risk. Indian J Med Paediatr Oncol. 2017;38(4):434-9. doi: 10.4103/ijmpo.ijmpo_168_16.

12. Padro T, Manfrini O, Bugiardini R, Canty J, Cenko E, De Luca G, et al. ESC Working Group on Coronary Pathophysiology and Microcirculation position paper on 'coronary microvascular dysfunction in cardiovascular disease'. Cardiovasc Res. 2020;116(4):741-55. doi: 10.1093/cvr/cvaa003.

13. Alokail MS, Al-Daghri N, Abdulkareem A, Draz HM, Yakout SM, Alnaami AM, et al. Metabolic syndrome biomarkers and early breast cancer in Saudi women: evidence for the presence of a systemic stress response and/or a pre-existing metabolic syndrome-related neoplasia risk? BMC Cancer. 2013;13:54. doi: 10.1186/1471-2407-13-54.

14. Boekel NB, Schaapveld M, Gietema JA, Russell NS, Poortmans P, Theuws JC, et al. Cardiovascular disease risk in a large, population-based cohort of breast cancer survivors. Int J Radiat Oncol Biol Phys. 2016;94(5):1061-72. doi: 10.1016/j.ijrobp.2015.11.040.

15. Jerusalem G, Moonen M, Freres P, Lancellotti P. The European Association of Cardiovascular Imaging/Heart Failure Association Cardiac Oncology Toxicity Registry: long-term benefits for breast cancer treatment. Future Oncol. 2015;11(20):2791-4. doi: 10.2217/fon.15.227.

16. Shum K, Solivan A, Parto P, Polin N, Jahangir E. Cardiovascular risk and level of statin use among women with breast cancer in a cardio-oncology clinic. Ochsner J. 2016;16(3):217-24.

17. Ortiz-Mendoza CM, de-la-Fuente-Vera TA, Pérez-Chávez E. Metabolic syndrome in Mexican women survivors of breast cancer: a pilot study at a general hospital. Med Arch. 2014;68(1):19-21. doi: 10.5455/medarh.2014.68.19-21.

18. Chen Y, Wen YY, Li ZR, Luo DL, Zhang XH. The molecular mechanisms between metabolic syndrome and breast cancer. Biochem Biophys Res Commun. 2016;471(4):391-5. doi: 10.1016/j.bbrc.2016.02.034.

19. Kim HJ, Kim HS, Kim HR, Yoo YS, Song BJ. Characterization of metabolic syndrome risk factors and health-related behaviors in korean patients with breast cancer by abdominal obesity status. J Nurs Res. 2020;28(2):74. doi: 10.1097/JNR.0000000000000345.

20. Lee K, Sami N, Tripathy D, Demark-Wahnefried W, Norris MK, Courneya KS, et al. Aerobic and resistance exercise improves Reynolds risk score in overweight or obese breast cancer survivors. Cardiooncology. 2020;6(1):27. doi: 10.1186/s40959-020-00084-6.

21. Berrino F, Villarini A, Traina A, Bonanni B, Panico S, Mano MP, et al. Metabolic syndrome and breast cancer prognosis. Breast Cancer Res Treat. 2014;147(1):159-65. doi: 10.1007/s10549-014-3076-6.

22. Tan CH, Chao TT, Liu JC, Lin CH, Huang YS, Chang CM, et al. Breast cancer therapy and age difference in cardiovascular disease risks: a population-based cohort study in Taiwan. Taiwan J Obstet Gynecol. 2016;55(1):98-103. doi: 10.1016/j.tjog.2015.12.005.

23. Guan T, Zhang H, Yang J, Lin W, Wang K, Su M, et al. Increased risk of cardiovascular death in breast cancer patients without chemotherapy or (and) radiotherapy: a large population-based study. Front Oncol. 2021;10:619622. doi: 10.3389/fonc.2020.619622.

24. Aldaz CM, Ferguson BW, Abba MC. WWOX at the crossroads of cancer, metabolic syndrome related traits and CNS pathologies. Biochim Biophys Acta. 2014;1846(1):188-200. doi: 10.1016/j.bbcan.2014.06.001.

25. Lahoz C, Valdivielso P, González-Alegre MT, García-Iglesias MF, Estirado E, Mostaza JM. Cancer and cardiovascular disease. Clin Investig Arterioscler. 2015;27(5):221-5. doi: 10.1016/j.arteri.2015.02.002.

26. Lubas MM, Wang M, Jefferies JL, Ness KK, Ehrhardt MJ, Krull KR, et al. The contribution of stress and distress to cardiovascular health in adult survivors of childhood cancer. Cancer Epidemiol Biomarkers Prev. 2021;30(2):286-94. doi: 10.1158/1055-9965.EPI-20-1183.

27. Felicetti F, Fortunati N, Brignardello E. Cancer survivors: an expanding population with an increased cardiometabolic risk. Diabetes Res Clin Pract. 2018;143:432-42. doi: 10.1016/j.diabres.2018.02.016.

28. Jensen MV, Rugbjerg K, Licht SF, Johansen C, Schmiegelow K, Andersen KK, et al. Endocrine late effects in survivors of cancer in adolescence and young adulthood: a danish population-based cohort study. JAMA Netw Open. 2018;1(2):e180349. doi: 10.1001/jamanetworkopen.2018.0349.

29. Vassallo P, Driver SL, Stone NJ. Metabolic syndrome: an evolving clinical construct. Prog Cardiovasc Dis. 2016;59(2):172-7. doi: 10.1016/j.pcad.2016.07.012.

ORIGINAL ARTICLE

Women Undergoing Mitral Valve Replacement: A Retrospective Analysis

Júlia Lasserre Moreira; Pedro Henrique Andrade Araújo Salvatore Barletta, José Augusto Baucia

Faculdade de Medicina da Bahia - Universidade Federal da Bahia, Salvador, BA – Brazil

Abstract

Background: Although cardiovascular disease is the leading cause of death in women, few data exist on risk factors and treatment of these diseases in women. This leads to a delay in the institution of appropriate therapies and worse outcomes in this population.

Objective: We aimed to identify predictors of morbidity and mortality in women undergoing isolated mitral valve replacement.

Methods: This was a retrospective cohort study with 104 women who underwent isolated mitral valve replacement at a referral hospital for treatment of cardiovascular diseases, performed from January 2011 to December 2016. Data were obtained from medical records. Statistical analysis was performed to calculate odds ratio, unpaired Student's t-test, and binary logistic regression. P values <0.05 were considered statistically significant.

Results: Mean age of patients was 43.73 (±13.85) years. Most patients had a diagnosis of rheumatic disease prior to surgery (76%; N=79). Mortality rate was 4.9% (N = 5). There was a statistically higher risk of death among patients with reduced ejection fraction (EF) (<50%) (OR = 14.833, 95% CI 2.183 - 100.778, P=0.001) and older age (P = 0.009). There was an inverse association between a previous diagnosis of rheumatic disease and death (OR = 0.064, 95% CI 0.007 - 0.606, P=0.002). Logistic regression showed reduced EF at preoperative evaluation as a predictor of death and a diagnosis of rheumatic disease as a protective factor.

Conclusion: Older age and reduced EF were associated with postoperative mortality. Reduced EF was a predictor of death, and rheumatic disease was associated with better surgical outcomes.

Keywords: Morbidity; Mortality; Thoracic Surgery; Mitral Valve; Women.

Introduction

Cardiovascular disease (CVD) is the leading cause of death in developed countries[1] and, in Brazil, despite regional differences, CVD kills more than any other cause.[2] CVD is also the leading cause of death among women, and usually occurs 7–10 years later than men.[1] However, the prevalence of this disease increases in the postmenopausal period, possibly due to the decrease in estrogen hormone levels.

There are few data in the literature about the assessment of risk factors and treatment of CVDs in women, as compared to men, including in Brazil. This leads to a delay in the institution of appropriate therapies, so that women often receive less aggressive treatments and are less likely than their male counterparts to be managed following recommended guidelines.[3]

Mitral valve disease is the most common valvular heart disease. In developing countries, the main cause of mitral valve stenosis is rheumatic fever, and mitral valve replacement is currently one of the most common

Júlia Lasserre Moreira
Medical student
Universidade Federal da Bahia - UFBA

Mailing Address: Júlia Moreira
Rua Fonte do Boi, 115. Postal Code: 41940-360, Salvador, BA – Brazil.
E-mail: julialasserrem@hotmail.com

DOI: https://doi.org/10.36660/ijcs.20200412

Manuscript received December 25, 2020; revised manuscript March 01, 2021; accepted March 09, 2021.

treatments for this condition.[4] Mitral stenosis and regurgitation may cause pulmonary hypertension and right heart failure, leading to poor outcomes.

Sex differences in outcomes have been noted in many areas of cardiovascular medicine, and this is not different in mitral valve disease, although the causes of such differences are not well understood.[5] Prior studies have hypothesized that differences in mitral valve morphology, complexity of lesions, timing of interventions, and comorbid conditions place female patients at a disadvantage at the time of surgery.[3] Although women are as likely to have significant mitral valve disease, they are less likely to receive surgery than male patients[6] and, when they do, operative mortality is higher among women undergoing mitral valve repair or replacement compared to men.[3]

The purpose of this article was to identify preoperative, intraoperative, and postoperative risk factors for morbidity and mortality in a Brazilian female group of patients who underwent isolated mitral valve replacement, to obtain pertinent information regarding the current scenario in Brazil and contribute to a more gender-specific and individualized treatment of women.

Methods

This was a retrospective cohort study that analyzed the medical records of patients who underwent isolated mitral valve replacement at a referral center for treatment of cardiovascular diseases located in the city of Salvador (Bahia, Brazil). Primary outcome was death in the postoperative period of isolated mitral valve surgery, and secondary outcome was incidence of morbidity.

Female patients who underwent isolated mitral valve replacement between 2011 and 2016, regardless of age, valve lesion etiology, or type of prosthesis, were included. Patients who underwent mitral valve replacement in combination with any other surgical procedure were excluded. Patients with missing information and those whose medical records were not available were also excluded.

Of 207 patients, 43 were excluded due to lack of information in the medical records, leaving 164 patients. Of these, 60 male patients were excluded, remaining 104 female patients for analysis.

Clinical and laboratory data from the preoperative, intraoperative, and postoperative periods were collected from medical records, using a standardized form. Table 1 lists all variables and outcomes investigated.

Statistical analysis

Statistical analysis was performed using the software IBM SPSS statistics for Windows, version 23.0. Categorical variables were presented as absolute and relative

Table 1 – Variables and outcomes evaluated in a sample of female patients (n=104) who underwent isolated mitral valve replacement between 2011 and 2016

1. Age	
2. Gender	
3. Height	
4. Weight	
5. Body mass index	
6. NYHA functional classification	
7. Preoperative comorbidities:	a. Stroke
	b. Diabetes mellitus
	c. Rheumatic fever
	d. Endocarditis
	f. Asthma
	g. Smoking
	h. Coronary artery disease
	i. Atrial fibrillation (AF)
	j. Chronic obstructive pulmonary disease
	k. Previous valve operation

Continuation

8. Urea	
9. Creatinine	
10. Hb (g/dl)	
11. Ht (%)	
12. Prothrombin time	
13. INR	
14. Rhythm of electrocardiogram	
15. Echocardiographic measurements	
16. EuroSCORE	
17. Urgency or elective surgery	
18. Prosthesis model	
19. Prosthesis size	
20. Mitral calcification	
21. Duration of extracorporeal circulation	
22. Aortic clamping time	
23. Length of ICU stay	
24. Outcomes:	a. Acute myocardial infarction
	b Stroke
	c. Respiratory tract infection
	d. Arrhythmia
	e. Reoperation
	f. Cardiac tamponade
	g. Hb (mg/dl)
	h. Mediastinitis
	i. Sepsis
	j Endocarditis
	k Other
	l. Death

EuroSCORE: European System for Cardiac Operative Risk Evaluation; Hb: hemoglobin; Ht: hematocrit; ICU: intensive care unit; INR: International Normalized Ratio; NYHA: New York Heart Association

frequencies, whereas continuous variables were presented as means and standard deviations. Associations between categorical variables were assessed by odds ratio (OR). The Kolmogorov-Smirnov test was used to evaluate the normality of data distribution. Means were compared using the unpaired Student's t-test.

Binary logistic regression was used to identify possible predictors of postoperative death, using Nagelkerke's coefficient of determination (R^2). P-values <0.05 were considered statistically significant.

Ethical considerations

This study was approved by the Research Ethics Committee of the *Ana Nery Hospital* (protocol no. 336.981, approved on July 19, 2013). In accordance with Resolution No. 466/2012 of the Brazilian National Commission for

Research Ethics on research involving human beings, this study protocol was registered on the *Plataforma Brasil* website (CAAE number 14268813.5.0000.0045). The authors signed a form to assure that patient data would be kept confidential. The standardized form used to collect patient information was approved by the local institutional review board.

Results

Mean age of the sample was 43.73 (±13.85) years. Mean body weight was 61.38 (± 12.02) kg, and mean body mass index was 24.44 (±4.46) kg/m². Thirty patients (28.8%) had no record of medication use, while 74 (71.2%) were on drug therapy, mostly diuretics (N=54; 51.9%) and betablockers (N=49; 47.1%). Nineteen patients (18.3%) had received penicillin. Preoperative evaluations indicated that 95.2% of the patients had at least one comorbidity, and most of them (N=79; 76%) had been diagnosed with rheumatic heart disease prior to surgery (Table 2).

Mitral repair had been performed in 18 (17.3%) patients and 9 (8.6%) had been submitted to mitral valve replacement. The mean European System for Cardiac Operative Risk Evaluation score (EuroSCORE) was 5.11 (±7.45). Laboratory test results prior to the mitral valve surgery are described in Table 3.

Most patients had sinus rhythm on preoperative electrocardiogram (N=48; 46.2%), with no other changes described. Thirty-five patients (33.7%) had atrial fibrillation (AF), one had (1.0%) atrial flutter, four (3.8%) had bradycardia, and three (2.9%) had tachycardia. Three patients (2.9%) had other cardiac alterations.

The most commonly reported valve dysfunction was mixed mitral valve lesions (N=43; 41.3%), followed by mitral valve regurgitation (N=38; 36.5%) and stenosis (N=15; 14.4%) (Figure 1). The most common valvular lesion was tricuspid regurgitation, found in 68 (65.4%) patients. In patients with valvular prosthesis, regurgitation (N=7; 77.8%) and mixed lesions (N=2; 22.2%) were observed.

Of the total number of patients, only one patient underwent urgent surgery. Biological prostheses were the most used prosthetic heart valves (N=72; 69.2%); the most common size of the prosthesis was 29 mm (N=49; 47.1%), followed by 31 mm (N=30; 28.8%) and 27 mm (N=9; 8.7%). Papillary muscle and chordae tendineae were preserved in all patients, whenever technically

Table 2 – Preoperative comorbidities of women undergoing isolated mitral valve replacement (n=104)

Comorbidities		Frequency
Rheumatic disease		79 (76.0%)
Hypertension		39 (37.5%)
Atrial fibrillation		36 (34.6%)
Smoking or former smoking		15 (14.4%)
Stroke		16 (15.4%)
Endocarditis		10 (9.6%)
Diabetes mellitus		12 (11.5%)
Asthma		5 (4.8%)
Coronary artery disease		4 (3.8%)
Chronic obstructive pulmonary disease		1 (1.0%)
NYHA functional class	1	2 (2.2%)
	2	44 (47.3%)
	3	36 (38.7%)
	4	11 (11.8%)

NYHA: New York Heart Association

Table 3 - Preoperative laboratory results of women undergoing isolated mitral valve replacement (n=104)

Exams	Mean (standard deviation)	Frequencies
Hemoglobin (g/dL)	12.09 (± 1.69)	-
Hematocrit (%)	36.26 (± 5.50)	-
Creatinine (mg/dL)	1.06 (± 0.73)	-
Urea (mg/dL)	34.47 (± 24.74)	-
International Normalized Ratio	1.43 (± 0.57)	-
Prothrombin time (%)	73.06 (± 26.31)	-
Left atrium (mm)	52.95 (± 16.24)	-
Aorta (mm)	28.66 (± 5.56)	-
LV systolic diameter (mm)	33.73 (± 8.66)	-
LV diastolic diameter (mm)	51.88 (± 9.28)	-
Posterior wall thickness (mm)	8.11 (± 1.86)	-
Interventricular septum (mm)	8.13 (± 1.83)	-
LV ejection fraction (%)	63.07 (± 10.86)	-
Pulmonary artery systolic pressure (mmHg)	48.75 (± 18.31)	-
Calcification	-	29 (27.9%)
Paravalvular leak	-	11 (10.6%)

LV: Left ventricular

possible. Prophylactic anticoagulation therapy for postoperative thrombosis was made immediately after drain removal.

The overall mortality rate was 4.9% (N=5), with sepsis as the leading cause of death (N=2; 40.0%), followed by tachyarrhythmia (N=1; 20.0%). One death was registered due to Chagasic cardiomyopathy (20%), and in one case, no specific cause of death was recorded. Three of the five patients who died had low left ventricular ejection fraction (LVEF) before surgery. The mean number of days the patients stayed in the intensive care unit was 5.24 (± 4.47) days, with a mean length of stay of four days.

The most common postoperative complications were arrhythmias (N=24; 23.1%), followed by respiratory tract infection (N=14; 13.5%) and renal failure (N=8; 7.7%) (Table 4). The most common arrhythmia was AF (N=18; 75.0%), followed by supraventricular tachycardia (N=2; 8.3%) and ventricular tachycardia (N=2; 8.3%). One case of atrial flutter and one of complete heart blockage were reported (4.2% for each).

Comparing the mean age of patients who died after surgery with those who survived, a statistically significant difference was observed, indicating that older age was associated with the primary outcome (Table 5). Low LVEF (< 50%) was associated with the risk of death in the postoperative period.

A previous diagnosis of rheumatic disease was associated with a reduced risk of postoperative mortality. However, these patients were significantly younger than those who did not receive this diagnosis (40.4 years vs. 54.2 years; P<0.001).

The presence of arrhythmias in the preoperative period was not associated with mortality after valve replacement (Table 6). The same was observed for patients with a previous diagnosis of hypertension, endocarditis, or stroke. Since no patient with diabetes, coronary artery disease, obesity (BMI > 30 kg/m^2), chronic obstructive pulmonary disease (COPD), or asthma died, it was impossible to establish associations of these variables with the primary outcome.

The New York Heart Association (NYHA) functional classes III/IV, previous mitral valve surgery, and type of heart valve disease were also not associated with higher mortality.

All variables that showed an association with mortality were submitted to multivariate analysis by binary logistic regression. A significant model was obtained with reduced LVEF (< 50%) and prior diagnosis of rheumatic disease as variable (χ^2 (2) = 14.262, P = 0.001; R^2 Nagelkerke = 0.402) (Table 7). The same did not happen for age.

Reduced ejection fraction was a predictor of postoperative death in the model, and a prior diagnosis of rheumatic disease was associated with better surgical outcomes.

Discussion

Rheumatic disease was the most frequent comorbidity in our sample. This was expected, since in underdeveloped and developing countries like Brazil, this disease remains endemic, and is the main etiology of valve dysfunction.[7-9] In addition, it is known that its prevalence is higher in the female population,[7] which has been confirmed by most studies on valve disease.[8, 11-16]

As observed in the present study, mean age of patients undergoing valve replacement due to rheumatic etiology is relatively low, in accordance with previous

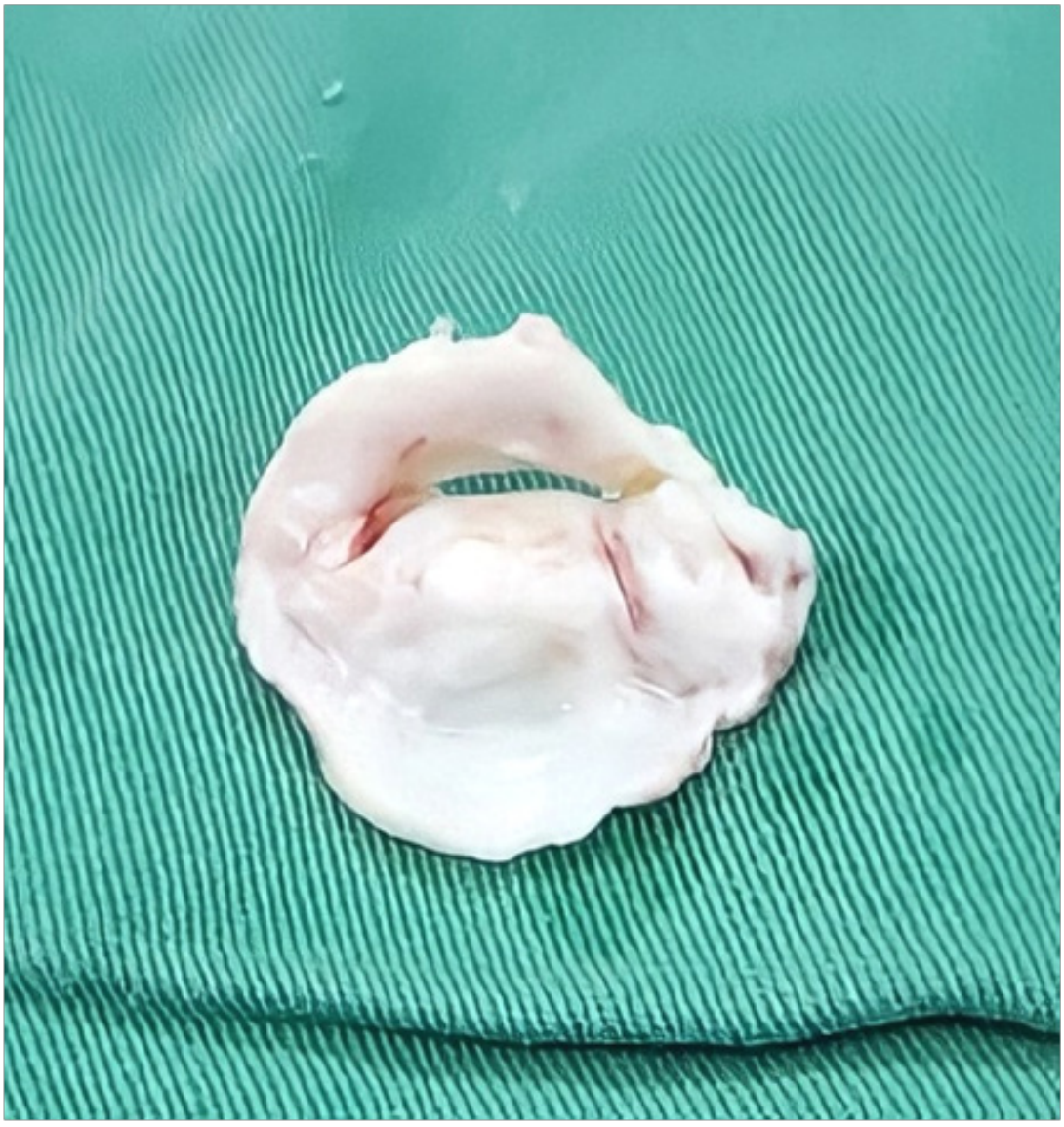


Figure 1 – Mitral valve with stenosis secondary to rheumatic disease

Table 4 – Postoperative outcomes of women undergoing isolated mitral valve replacement (n=104)

Outcomes	Frequencies
Arrhythmias	24 (23.1%)
Respiratory tract infection	14 (13.5%)
Renal insufficiency	8 (7.7%)
Death	5 (4.9%)
Pericardial effusion	3 (2.9%)
Surgical wound infection	5 (4.8%)
Sepsis	4 (3.8%)
Pleural effusion	3 (2.9%)
Mediastinitis	4 (3.8%)
Reoperation	4 (3.8%)
Urinary tract infection	3 (2.9%)
Cardiac tamponade	1 (1.0%)
Endocarditis	2 (1.9%)
Subcutaneous emphysema	0 (0.0%)
Stroke	0 (0.0%)
Pneumothorax	0 (0.0%)
Acute heart failure	0 (0.0%)
Pulmonary thromboembolism	1 (1.0%)

studies.[12,15,17] On the other hand, participants of studies carried out in high-income countries are older, due to the predominance of degenerative and ischemic etiology of valve disease.[10,19]

Studies have shown that mortality of cardiac surgery among women is higher than of their male counterparts,[3,5,6,11,20-22] since women receive surgery late and usually have more severe preoperative conditions.[3,6,11,21,23] One of the possibilities for this fact is the use of cutoff points for echocardiographic variables without considering their body mass, which is generally lower than men's. Others have postulated about the differences in symptom manifestation, anatomical or even pathophysiological features. In this study, however, mortality rate was within normal range (4 to 7%),[24] similarly to previous reports.[10,19,25]

The most frequent postoperative complications were arrhythmias, respiratory tract infections and renal failure, which are commonly and classically found after heart and valve surgeries.[16,19,22,26] The main causes of death were also in accordance with the literature. Also, although some studies have shown a predominance of cardiac[22, 25] or infectious[27] causes alone, generally both, as well as neurological events, are also common, as seen in the present study.[16, 19, 22, 25,27]

There is considerable controversy about the risk factors associated with mortality after valve replacement surgery. Results have varied widely according to the population and the study method. Age, for example, has already been associated with higher mortality in several studies, as well as in ours.[3,10, 12, 16,22,28-31]. However, this is still not a consensus, since others have found no difference between groups,[25, 32] or even an inverse relationship.[19,23,33]

There are no records of the influence of rheumatic disease on postoperative outcomes. Khan *et* al.[17] showed a correlation between high levels of anti-streptolysin O and mortality. However, this is a marker of the acute phase of rheumatic fever, rather than its sequel. We found in this study that a history of rheumatic disease was a protective factor, associated with lower immediate mortality. We emphasize,

Table 5 – Odds ratio values representative of risk-related outcomes in a sample of female patients (n=104) who underwent isolated mitral valve replacement between 2011 and 2016

Variable	N (%)	Deaths	Odds ratio	95% confidence interval	p-value
Obesity (BMI > 30 kg/m2)	11 (12.4%)	0 (0.0%)	-	-	0.508
Arrhythmias	46 (49.5%)	4 (8.7%)	4.381	0.471 - 40.778	0.160
NYHA functional class III/IV	47 (50.5%)	2 (4.3%)	0.978	0.132 - 7.250	0.982
Stroke	16 (15.5%)	1 (6.3%)	1.383	0.144 - 13.247	0.777
Rheumatic disease	79 (76.7%)	1 (1.3%)	0.064	0.007 - 0.606	0.002
Chronic obstructive pulmonary disease	1 (1.0%)	0 (0.0%)	-	-	0.820
Coronary artery disease	4 (3.9%)	0 (0.0%)	-	-	0.645
Diabetes	12 (11.7%)	0 (0.0%)	-	-	0.405
Hypertension	39 (37.9%)	2 (5.1%)	1.099	0.175 - 6.887	0.920
Asthma	5 (4.9%)	0 (0.0%)	-	-	0.605
Smoking	15 (14.6%)	0 (0.0%)	-	-	0.344
Atrial fibrillation	36 (35.0%)	2 (5.6%)	1.255	0.200 - 7.877	0.808
Endocarditis	9 (8.7%)	1 (11.1%)	2.813	0.280 - 28.264	0.361
Previous valve surgery	39 (37.9%)	1 (2.6%)	0.395	0.043 - 3.666	0.399
Urgent surgery	1 (1.0%)	0 (0.0%)	-	-	0.839
Mitral calcification	29 (28.2%)	1 (3.4%)	0.625	0.067 - 5.840	0.678
LV ejection fraction	12 (11.7%)	3 (25.0%)	14.833	2.183 - 100.778	0.001
Mitral regurgitation	37 (35.9%)	3 (8.1%)	2.824	0.450 - 17.724	0.250
Mitral stenosis	15 (14.6%)	0 (0.0%)	-	-	0.344
Mixed mitral lesion	43 (41.7%)	2 (4.7%)	0.927	0.148 - 5.799	0.935
Lesions in other valves	81 (79.4%)	5 (6.2%)	-	-	0.243
Paravalvular leak	10 (9.7%)	0 (0.0%)	-	-	0.452

BMI: Body Mass Index; NYHA: New York Heart Association; LV: Left Ventricular

however, that the group with this disease was younger, which may have influenced the results. On the other hand, the multivariate analysis did not reveal a significant effect of age.

Atrial fibrillation is often found in patients with mitral disease and the prevalence of this arrhythmia in our sample is compatible with what has been found previously.[12,15] The role of this arrhythmia in surgical outcomes, however, is still controversial. While some studies have not demonstrated an association between atrial fibrillation and unfavorable outcomes,[32,34] as described in this article, others have shown that it is a risk factor.[16,19,27,29, 31, 35]

We did not find any relationship between any other preoperative variable (diagnoses or laboratory findings) and higher mortality, which is in line with results reported by Fernandes *et* al.[28] and De Bacco *et* al.[32] However, previous publications have reported an association of elevated BMI values,[10,26] history of coronary artery disease,[16,22,30,33] endocarditis,[22] stroke[30], hypertension and COPD[19] with postoperative complications and death. Among laboratory variables, elevations in creatinine / kidney injury[17,19,22,32] and reduced hemoglobin and hematocrit values[28] have already been reported as risk factors, which was not observed in this study.

Table 6 – Comparisons of numerical variables between survivors and non-survivors patients after isolated mitral valve replacement

Variable	Total	Non-survivors	Survivors	p-value
Age	43.73 ± 13.85	59.40 ± 11.06	43.07 ± 13.56	0.009
BMI	24.44 ± 4.46	25.63 ± 4.25	24.46 ± 4.46	0.655
Days in ICU	5.24 ± 4.47	15.50 ± 16.30	4.84 ± 2.85	0.282
Preoperative Hb (g/dl)	12.09 ± 1.69	11.47 ± 2.94	12.14 ± 1.62	0.640
Preoperative Ht (%)	36.27 ± 5.50	35.18 ± 9.82	36.36 ± 5.28	0.802
Preoperative Cr (mg/dL)	1.06 ± 0.73	0.94 ± 0.85	1.07 ± 0.74	0.694
Preoperative Ur (mg/dL)	34.47 ± 24.74	80.48 ± 80.17	32.13 ± 16.10	0.249
INR	1.43 ± 0.57	1.57 ± 0.80	1.43 ± 0.56	0.638
PT (%)	73.06 ± 26.31	68.20 ± 33.24	73.22 ± 26.22	0.681
Left atrium (mm)	52.95 ± 16.24	66.25 ± 18.23	52.41 ± 16.03	0.095
Aorta (mm)	28.66 ± 5.56	30.00 ± 4.97	28.59 ± 5.60	0.623
LV diastolic diameter (mm)	51.88 ± 9.28	53.13 ± 9.97	51.83 ± 9.30	0.786
LV systolic diameter (mm)	33.73 ± 8.66	32.90 ± 1.47	33.76 ± 8.84	0.846
Interventricular septum (mm)	8.13 ± 1.83	6.30 ± 3.77	8.21 ± 1.69	0.387
Systolic pulmonary artery pressure (mmHg)	48.75 ± 18.31	51.75 ± 10.11	48.60 ± 18.64	0.739
LV ejection fraction (%)	63.06 ± 10.86	50.15 ± 19.34	63.72 ± 9.98	0.193
Posterior wall thickness (mm)	8.11 ± 1.86	5.33 ± 4.04	8.21 ± 1.71	0.343
EuroSCORE	5.11 ± 7.45	11.08 ± 9.08	4.85 ± 7.30	0.069
Postoperative Hb (g/dl)	9.38 ± 1.62	9.56 ± 2.26	9.37 ± 1.60	0.799
Cardiopulmonary bypass length	73.97 ± 20.21	89.00 ± 41.29	73.29 ± 18.70	0.444
Myocardial anoxia	56.15 ± 16.54	62.20 ± 27.55	56.00 ± 15.94	0.643

BMI: Body Mass Index; ICU: Intensive Care Unit; Hb: hemoglobin; Ht: Hematocrit; Ur: urea; Cr: Creatinine; INR: International Normalized Ratio; PT: Prothrombin Time; LV: Left Ventricular; Student's tttest for numerical variables

Table 7 – Predicting variables of postoperative death

R^2 = 0.402 (Nagelkerke)		B	Significance	OR	95% CI to OR	
$\chi^2(2)$ = 14.262, P = 0.001					Inferior	Superior
Variables	Low ejection fraction	2.795	0.012	16.367	1.860	144.024
	Rheumatic disease	-2.832	0.022	0.059	0.005	0.660
	Constant	2.458	0.027	-	-	-

R^2: determination coefficient; χ^2: chi square; CI: confidence interval; OR: Odds ratio

The severity of symptoms according to the NYHA functional classification was not related to worse outcomes, which is in accordance with the study by De Bacco *et al*.[32] This contrasts with most previous studies[10, 12, 24, 28-30] although none of them had a similar sample to ours, i.e., with a predominance of females and rheumatic disease as the main etiology of the disease.

As previously found, lower LVEF was associated with higher mortality.[17, 22, 29-32] This result is understandable, given that patients with impaired cardiac function tend to have more complications in the postoperative period. However, other echocardiographic variables did not show a correlation with worse outcomes, as previously described.[28,30,31]

In our study, characteristics related to surgery, such as urgency, type of valve prosthesis, type of valve disease, or cardiopulmonary bypass and aortic clamping times did not show any influence on mortality. Among these, while some studies[10,30] have suggested the use of bioprosthesis as a risk factor, several others have not observed worse outcomes with its use, as we have seen in the present study.[13, 18, 24, 32] It is noteworthy that biological valves have been more frequently used than mechanical ones. The latter require anticoagulation for life, with strict control of INR, and consequently require access to health services and good treatment adherence. Unfortunately, the patients of our sample would probably have difficulty accessing health care after surgery. Thus, probably, the choice of the type of prosthesis was based not only on technical but also on socioeconomic issues, and the decision was made by the medical staff and the patient.

Kim *et al*.[16] and Cruz *et* al.[36] have demonstrated severe tricuspid regurgitation as a risk factor, and Rankin *et al*.[22] and De Bacco *et al*.,[32] respectively, have identified a history of previous valve surgery, and urgency of surgery as risk factors. Elevated cardiopulmonary bypass and aortic clamping times have already been described by Bueno *et al*.[29] However, we could not demonstrate such associations, which is in accordance with results reported in other studies.

We found a long average intensive care unit stay (5.34 days). This can be explained by the discharge protocol, in addition to the occurrence of complications such as acute renal failure, reoperations and infections, as seen in Table 4.

As limitations, it is worth mentioning that the study is retrospective and was performed at a single center. Data were obtained from medical records and the results may have been influenced by problems in data recording. Our sample had a limited number of patients, which may have prevented detection of statistical significance in some situations. For those reasons, we must have caution in making population inferences. It is also good to remember that Brazil is a heterogeneous country, and the study was performed in a single location, where rheumatic disease is still endemic and responsible for most of the cases referred to surgery for mitral disease. These results should not be extrapolated to other regions.

Conclusion

Advanced age and reduced LVEF at preoperative evaluation were associated with a greater risk of mortality in women undergoing isolated mitral valve replacement. Rheumatic disease was associated with better surgical outcomes.

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 *Hospital Ana Nery* under the protocol number 336.981. 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.

Author contributions

Conception and design of the research: Baucia JA, Moreira JL. Acquisition of data: Moreira JL. Analysis and interpretation of the data: Barletta PH, Moreira JL. Statistical analysis: Barletta PH. Writing of the manuscript: Baucia JA, Moreira JL, Barletta PH. Critical revision of the manuscript for intellectual content: Moreira, JL.

References

1. Masjedi S, Ferdous Z. Understanding the Role of Sex in Heart Valve and Major Vascular Diseases. Cardiovasc Eng Technol. 2015;6(3):209-19. doi: 10.1007/s13239-015-0226-x.
2. Ferreira LCM, Nogueira MC, Carvalho MS, Teixeira MTB. Mortality Due to Acute Myocardial Infarction in Brazil from 1996 to 2016: 21 Years of Disparities in Brazilian Regions. Arq Bras Cardiol. 2020;115(5):849-859. doi: 10.36660/abc.20190438.
3. Adigun RO, Boler AN, Mankad R. Disparities in Cardiac Care of Women: Current Data and Possible Solutions. Curr Treat Options Cardiovasc Med. 2018;20(11):87. doi: 10.1007/s11936-018-0688-x.
4. Nishimura RA, Vahanian A, Eleid MF, Mack MJ. Mitral valve disease--current management and future challenges. Lancet. 2016;387(10025):1324-34. doi: 10.1016/S0140-6736(16)00558-4.
5. Seeburger J, Eifert S, Pfannmüller B, Garbade J, Vollroth M, Misfeld M, Borger M, Mohr FW. Gender differences in mitral valve surgery. Thorac Cardiovasc Surg. 2013;61(1):42-6. doi: 10.1055/s-0032-1331583.
6. McNeely C, Vassileva C. Mitral Valve Surgery in Women: Another Target for Eradicating Sex Inequality. Circ Cardiovasc Qual Outcomes. 2016;9(2 Suppl 1):S94-6. doi: 10.1161/CIRCOUTCOMES.115.002603.
7. Zühlke L, Karthikeyan G, Engel ME, Rangarajan S, Mackie P, Cupido-Katya Mauff B, et al. Clinical Outcomes in 3343 Children and Adults With Rheumatic Heart Disease From 14 Low- and Middle-Income Countries: Two-Year Follow-Up of the Global Rheumatic Heart Disease Registry (the REMEDY Study). Circulation. 2016;134(19):1456-1466. doi: 10.1161/CIRCULATIONAHA.116.024769.
8. Zilli AC, Guizilini S, Rocco IS, Santo JADE, Berwanger O, Kalil RAK, et al. Valve Heart Surgery in Brazil - The BYPASS Registry Analysis. Braz J Cardiovasc Surg. 2020;35(1):82-90. doi: 10.21470/1678-9741-2019-0408.
9. Remenyi B, ElGuindy A, Smith SC Jr, Yacoub M, Holmes DR Jr. Valvular aspects of rheumatic heart disease. Lancet. 2016;387(10025):1335-46. doi: 10.1016/S0140-6736(16)00547-X.
10. Jamieson WR, Germann E, Ye J, Chan F, Cheung A, MacNab JS, et al. Effect of prosthesis-patient mismatch on long-term survival with mitral valve replacement: assessment to 15 years. Ann Thorac Surg. 2009;87(4):1135-41. doi: 10.1016/j.athoracsur.2009.01.056.
11. Nitsche C, Koschutnik M, Kammerlander A, Hengstenberg C, Mascherbauer J. Gender-specific differences in valvular heart disease. Wien Klin Wochenschr. 2020;132(3-4):61-68. doi: 10.1007/s00508-019-01603-x.
12. Bourguignon T, Espitalier F, Pantaleon C, Vermes E, El-Arid JM, Loardi C, et al. Bioprosthetic mitral valve replacement in patients aged 65 years or younger: long-term outcomes with the Carpentier-Edwards PERIMOUNT pericardial valve. Eur J Cardiothorac Surg. 2018;54(2):302-309. doi: 10.1093/ejcts/ezy029.
13. Fernandes AM, Pereira FS, Bitencourt LS, Pereira Neto AV, Bastos GB, Durães AR, et al. Aras R Jr, Lessa IN. Influence of valve prosthesis type on early mortality in patients undergoing valve surgery. Rev Bras Cir Cardiovasc. 2014;29(4):559-63. doi: 10.5935/1678-9741.20140035.
14. Severino ES, Petrucci O, Vilarinho KA, Lavagnoli CF, Silveira Filho Lda M, Oliveira PP, et al. Late outcomes of mitral repair in rheumatic patients. Rev Bras Cir Cardiovasc. 2011;26(4):559-64. doi: 10.5935/1678-9741.20110045.
15. Zadok OIB, Sagie A, Vaturi M, Shapira Y, Schwartzenberg S, Kuznitz I, et al. Long-Term Outcomes After Mitral Valve Replacement and Tricuspid Annuloplasty in Rheumatic Patients. Ann Thorac Surg. 2019;107(2):539-545. doi: 10.1016/j.athoracsur.2018.09.012.
16. Kim JB, Kim HJ, Moon DH, Jung SH, Choo SJ, Chung CH, et al. Long-term outcomes after surgery for rheumatic mitral valve disease: valve repair versus mechanical valve replacement. Eur J Cardiothorac Surg. 2010;37(5):1039-46. doi: 10.1016/j.ejcts.2009.11.019.
17. Khan MF, Khan MS, Bawany FI, Dar MI, Hussain M, Farhan S, et al. Predictors of Mortality in Patients Undergoing Mitral Valve Replacement. Glob J Health Sci. 2015;8(3):37-42. doi: 10.5539/gjhs.v8n3p37.
18. Chikwe J, Chiang YP, Egorova NN, Itagaki S, Adams DH. Survival and outcomes following bioprosthetic vs mechanical mitral valve replacement in patients aged 50 to 69 years. JAMA. 2015;313(14):1435-42. doi: 10.1001/jama.2015.3164.
19. Murana G, Alfonsi J, Savini C, Mariani C, Coppola G, Lo Coco V, et al. On-X mitral valve replacement: a single-centre experience in 318 patients. Interact Cardiovasc Thorac Surg. 2018;27(6):836-841. doi: 10.1093/icvts/ivy184.
20. Giustino G, Overbey J, Taylor D, Ailawadi G, Kirkwood K, DeRose J, et al. Sex-Based Differences in Outcomes After Mitral Valve Surgery for Severe Ischemic Mitral Regurgitation: From the Cardiothoracic Surgical Trials Network. JACC Heart Fail. 2019;7(6):481-490. doi: 10.1016/j.jchf.2019.03.001.
21. Crousillat DR, Wood MJ. Valvular Heart Disease and Heart Failure in Women. Heart Fail Clin. 2019;15(1):77-85. doi: 10.1016/j.hfc.2018.08.008.
22. Rankin JS, Hammill BG, Ferguson TB Jr, Glower DD, O'Brien SM, DeLong ER, et al. Determinants of operative mortality in valvular heart surgery. J Thorac Cardiovasc Surg. 2006;131(3):547-57. doi: 10.1016/j.jtcvs.2005.10.041.
23. Chan V, Chen L, Elmistekawy E, Ruel M, Mesana TG. Determinants of late outcomes in women undergoing mitral repair of myxomatous degeneration. Interact Cardiovasc Thorac Surg. 2016;23(5):779-783. doi: 10.1093/icvts/ivw222.
24. van der Merwe J, Casselman F. Mitral Valve Replacement-Current and Future Perspectives. Open J Cardiovasc Surg. 2017;9:1179065217719023. doi: 10.1177/1179065217719023 19023.
25. Appelbaum A, Kouchoukos NT, Blackstone EH, Kirklin JW. Early risks of open heart surgery for mitral valve disease. Am J Cardiol. 1976;37(2):201-9. doi: 10.1016/0002-9149(76)90313-1.
26. Laizo A, Delgado FE, Rocha GM. Complications that increase the time of Hospitalization at ICU of patients submitted to cardiac surgery. Rev Bras Cir Cardiovasc. 2010;25(2):166-71. doi: 10.1590/s0102-76382010000200007.
27. Eguchi K, Ohtaki E, Matsumura T, Tanaka K, Tohbaru T, Iguchi N, et al. Pre-operative atrial fibrillation as the key determinant of outcome of mitral valve repair for degenerative mitral regurgitation. Eur Heart J. 2005;26(18):1866-72. doi: 10.1093/eurheartj/ehi272.
28. Fernandes AM, Andrade GM, Oliveira RM, Biscaia GT, Reis FF, Macedo CR, et al. Evaluation of variables responsible for hospital mortality in patients with rheumatic heart disease undergoing double valve replacement. Rev Bras Cir Cardiovasc. 2014;29(4):537-42. doi: 10.5935/1678-9741.20140044.
29. Bueno RM, Ávila Neto V, Melo RFA. Fatores de risco em operações valvares: análise de 412 casos. Braz J Cardiovasc Surg. 199;12(4):348-358. doi: 10.1590/S0102-76381997000400007.
30. Lam BK, Chan V, Hendry P, Ruel M, Masters R, Bedard P, et al. The impact of patient-prosthesis mismatch on late outcomes after mitral valve replacement. J Thorac Cardiovasc Surg. 2007;133(6):1464-73. doi: 10.1016/j.jtcvs.2006.12.071..
31. Wang B, Xu ZY, Han L, Zhang GX, Lu FL, Song ZG. Impact of preoperative atrial fibrillation on mortality and cardiovascular outcomes of mechanical mitral valve replacement for rheumatic mitral valve disease. Eur J Cardiothorac Surg. 2013;43(3):513-9. doi: 10.1093/ejcts/ezs213.
32. De Bacco MW, Sartori AP, Sant'Anna JR, Santos MF, Prates PR, Kalil RA, et al. Risk factors for hospital mortality in valve replacement with mechanical prosthesis. Rev Bras Cir Cardiovasc. 2009;24(3):334-40. doi: 10.1590/s0102-76382009000400012.
33. Johnston A, Mesana TG, Lee DS, Eddeen AB, Sun LY. Sex Differences in Long-Term Survival After Major Cardiac Surgery: A Population-Based Cohort Study. J Am Heart Assoc. 2019;8(17):e013260. doi: 10.1161/JAHA.119.013260.

34. Lim E, Barlow CW, Hosseinpour AR, Wisbey C, Wilson K, Pidgeon W, et al. Influence of atrial fibrillation on outcome following mitral valve repair. Circulation. 2001;104(12 Suppl 1):59-63. doi: 10.1161/hc37t1.094813.

35. Rahimtoola SH. Choice of prosthetic heart valve in adults an update. J Am Coll Cardiol. 2010;55(22):2413-26. doi: 10.1016/j.jacc.2009.10.085.

36. Cruz RCC, Cordeiro BS, Santos FS, Fernandes CR, Gama JMA, Ladeia AMT. Predictors of Unfavourable Outcomes in Children and Adolescents Submitted to Surgical Mitral Valvuloplasty Secondary to Chronic Rheumatic Heart Disease. Arq Bras Cardiol. 2019;113(4):748-756. doi: 10.5935/abc.20190184.

37. Lampert BC, Lindenfeld J, Abraham WT. Too Different or Too Late?: Gender Differences in Outcomes After Mitral Valve Surgery. JACC Heart Fail. 2019;7(6):491-492. doi: 10.1016/j.jchf.2019.03.015.

ORIGINAL ARTICLE

Early Use of Handgrip Exercise Associated with Dobutamine Stress Echocardiography in Women

Isabela de Andrade Lindner, Patricia Sens de Oliveira, Caroline de Oliveira Fischer Bacca, Josie Budag Matsuda, Franciani Rodrigues da Rocha, Jeancarlo Visentainer, Luiz Eduardo Bacca

UNIDAVI - Centro Universitário para o Desenvolvimento do Alto Vale do Itajaí, Rio do Sul, SC – Brazil

Abstract

Background: Coronary artery disease (CAD) is an important cause of morbidity and mortality in women and requires early diagnosis for defining the appropriate treatment.

Objective: To identify the positive predictive value (PPV) and safety of the early use of handgrip exercise in pharmacological stress echocardiography using dobutamine (early-ECHO) in women.

Methods: Positive ischemic early-ECHO records from 111 women were evaluated from January 2012 to March 2018. Subsequently, the hospital medical records were verified to locate patients who underwent conventional coronary angiography (CCA), and we analyzed the medical conduct adopted for these patients. Statistical analyses were performed using SPSS employing one-way analysis of variance (ANOVA), Fisher's exact test, or Pearson's chi-square test. The level of statistical significance was set at $p < 0.05$ for all analyses.

Results: Four patients (4.4%) presented serious complications during the examination. Out of 90 patients who underwent CCA, 71 (78.9%) had CAD. Among these 71 patients, 58 (81.7%) had severe lesions and 13 (18.3%) presented moderate CAD. Moreover, CCA did not demonstrate relevant coronary lesions in 19 of the 90 patients (21.1%). Among patients with severe CAD, 16 (27.6%) underwent myocardial revascularization surgery; 34 (58.6%) underwent percutaneous coronary angioplasty; and 08 (13.7%) had their clinical treatments intensified. The PPV for early-ECHO was 78.9%.

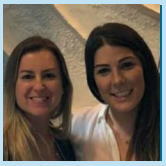
Conclusions: Early-ECHO showed a high PPV for diagnosing myocardial ischemia in women. It presented a low complication rate and provided rapid disease identification, allowing the early treatment of injuries and potentially preventing CAD complications.

Keywords: Stress Echocardiography; Coronary Artery Disease; Women; Predictive Value of Tests; Safety.

Introduction

Ischemic heart disease is an important public health problem in Brazil. Between 2008 and 2018, 488 858 deaths of women due to coronary artery disease (CAD) were reported.[1] According to the American Heart Association (AHA), approximately 1 in 3 women have some form of cardiovascular disease. The evidence shows that women at risk for CAD are less often referred to appropriate diagnostic tests than men.[2]

Clinical presentations of CAD result from atherosclerosis of the coronary arteries and overt angina syndromes, acute myocardial infarction, ischemic cardiomyopathy, and sudden cardiac death. A major aggravating factor in the



Patrícia Sens de Oliveira and Isabela de Andrade Lindner
Medicine Students
UNIDAVI (Centro Universitário para o Desenvolvimento do Alto Vale) Rio do Sul - SC

Mailing Address: Caroline Fischer Bacca
Rua Guilherme Gemballa, 13. Postal Code: 89160-932, Jardim América, Rio do Sul, SC – Brazil.
E-mail: caroline.bacca@unidavi.edu.br

DOI: https://doi.org/10.36660/ijcs.20200420

Manuscript received December 31, 2020; revised manuscript March 18, 2021; accepted May 18, 2021.

occurrence of CAD is its silent characteristic, which can be perceived at certain effort levels when there is an increase in myocardial oxygen consumption (MVO2).[3,4]

In this context, diagnostic tests increase the scope for investigating ischemia. Dobutamine stress echocardiography is an affordable, non-invasive, radiation-free test that allows the assessment of several segments of the left ventricle, making it possible to assess a patient's risk of developing severe CAD.[4]

Currently, the use of the 3-minute dobutamine protocol has become a popular noninvasive technology (NIT), with the addition of atropine at the final stage.[5] However, atropine may prolong exam time and cause serious side effects.[6,7]

The use of isometric handgrip exercise with dobutamine-atropine stress echocardiography (early-ECHO) decreases the time to target heart rate, recovery time, and the overall examination time.[8] Another advantage of early-ECHO is the reduction of the total dose infusion of dobutamine and its consequent side effects.[9]

Adjunctive isometric exercise in the form of sustained submaximal handgrip dobutamine stress echocardiography without atropine results in a modest increase in MVO2, primarily by an increase in end-systolic wall stress;[10] it can also significantly lower fractional flow reserve (FFR) values and potentially improve the ability of this test to detect physiologically significant stenosis.[11]

The main goal of this study was to highlight the positive predictive value (PPV) of early-ECHO in detecting CAD in women, emphasizing its safety and applicability.

Methods

Participants

This study analyzed the medical records of female patients subjected to pharmacological stress echocardiography with dobutamine with an early protocol (early-ECHO) at a diagnostic imaging center from January 2012 to March 2018.

Secondary data collected from medical records of patients at the imaging center were compared with those of the region's referral hospital in the same period. Data from the center's medical records included age, body mass index (BMI), incidence of complications during the examination (complex ventricular arrhythmia, arterial hypertension above 220/110 mmHg, and/or angina chest pain), and dobutamine dosages used in the procedure. Data obtained from the hospital's medical records, on the other hand, were used to refer to a conventional coronary angiography (CCA) examination and demonstrate the accuracy of positive early-ECHO results, as well as to quantify blood vessel occlusion and the medical conduct adopted for treating patients.

Inclusion criteria were defined by early-ECHO tests in which a positive ischemia response was observed; exclusion criteria considered tests with a negative ischemia response. At one point, patients who did not undergo CCA at the referral hospital were excluded.

To evaluate the safety and PPV of early-ECHO, we selected the results of 111 patients with positive diagnostic tests. This validation was performed through the search for medical records of these patients at the hospital, followed by an analysis of the CCA examination.

The early-ECHO protocol

Two-dimensional transthoracic echocardiography with Doppler ultrasound was performed by an experienced certified sonographer-physician using a Phillips Affiniti 70 ultrasound. All patients were examined in the left lateral position.

Dobutamine was diluted in 5% glycated serum and administered through an infusion pump at doses of 5–10–20–40 mcg/kg/min, increasing every 3 minutes. Blood pressure (BP) and a 12-lead electrocardiogram (ECG) were acquired every 3 minutes, before increasing the medication dose. At the end of the examination, intravenous beta-blockers (5 mg metoprolol) were administered.

Moreover, in our early-ECHO protocol, isometric exercise (with a handgrip strengthener) was used from the third minute of the examination, when dobutamine dose was 10 mcg/kg/min. Firstly, the isometric strength exercise was used in the non-dominant hand and, after BP verification, the isometric strength intensity was increased for both hands in order to reach 85% of the maximum heart rate (MHR) estimated for a patient of that age or the optimization of a positive ischemia result.

Video records were captured at baseline, with a low dobutamine dose (5 to 10 mcg/kg/min), at peak stress (85% of MRH), and in the recovery phase (after using the beta-blocker). Images were selected from 4 different echocardiographic views: parasternal long axis, parasternal short axis, apical 4-chamber, and apical 2-chamber.

The early-ECHO protocol was first suggested by Yao and colleagues in 2003[8] and was adapted to the patients in this study as shown in Figure 1.

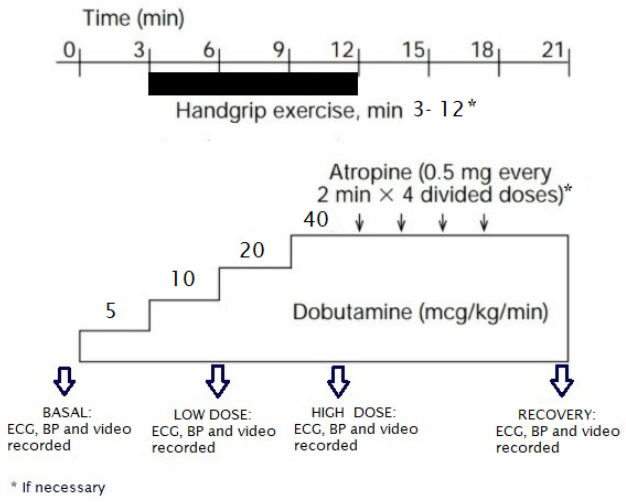


Figure 1 – Early pharmacological stress echocardiogram protocol. Adapted from Yao and colleagues, 2003.[8]
ECG: electrocardiogram; BP: blood pressure.

The presence of ischemia (positive test) was defined as the development of a new wall motion abnormality or worsening of an existing one during stress (hypokinesia, akinesia, or dyskinesia). When the examination demonstrated precocious contractile change, it was interrupted even without reaching the recommended MHR. For interpretive analyses, the left ventricle was divided into 17 segments as recommended by the American Society of Echocardiography.[12]

CCA

CCA still plays a pivotal role in the invasive imaging of coronary arteries. Despite rapid developments in noninvasive imaging, the temporal and spatial resolution of coronary angiography is unsurpassed and will remain as the road map for cardiology interventionalists and cardiac surgeons for performing revascularization.[13]

The purpose of CCA is to evaluate the coronary anatomy and the degree of luminal obstruction of the coronary arteries.[14] Angiographically normal or near-normal coronary arteries are more common among women, who are more likely than men to have myocardial ischemia due to microvascular disease.[15]

The degree of coronary stenosis has been determined by the AHA Guideline as: negative (without coronary lesion); discrete (less than 50% of stenosis); moderate (between 50% and 70% of luminal narrowing); and severe (more than 70% of luminal narrowing).[16]

Statistical analysis

The extracted data were organized using Microsoft Excel and then transferred to the SPSS software version 22.0, which was used for statistical analyses.

The Komogorov-Smirnov normality test was initially performed for quantitative variables. Given the normality of the findings, a one-way analysis of variance (ANOVA) parametric test was selected for comparing results and verifying statistical inferences. A Tukey's post hoc test was not used because no statistically significant difference was observed.

Quantitative variables are presented as mean values ± standard deviations. Qualitative variables are presented by n (absolute number) and % (percentage), and Fisher's exact test (if more than 20% of the expected value < 5) or Pearson's chi-squared test (if expected frequency > 5) were used as measures of association. In case of a statistically significant difference, the adjusted residuals analysis was used. In this analysis, statistical significance was considered where the frequency was higher (residual equal to or higher than +1.96) and where the frequency was lower (residual equal to or less than -1.96).

In order to determine PPV, the following formula was used: PPV = True Positive / (True Positive + False Positive). A p-value $\alpha = 0.05$ ($p < 0.05$) was adopted as the level of statistical significance in all analyses.

Results

Patient population

Out of 111 selected patients, 21 medical records were excluded since the CCA examinations had not been performed at the hospital. A total of 90 female patients met all inclusion criteria. The association between CCA outcomes and the variables analyzed in the study is shown in Table 1.

The mean age was 66.59 ± 9.86 years (p = 0.91), ranging from 43 to 98 years. No significant difference was observed in the patients' ages and the presence of CAD. Considering the BMI of these women, 37 (41.1%) were classified as overweight.

Furthermore, out of 90 patients who underwent CCA, 71 (78.9%) presented CAD; among these 71 patients, 13 (18.3%) had moderate CAD and 58 (81.7), severe CAD. Concerning all 90 patients, 19 (21.1%) had negative tests, without significant

Table 1 – Catheterization outcomes (conventional coronary angiography, CCA) compared with the variables analyzed before and during the examination (n = 90)

Variables	Negative n (%)	Mild stenosis n (%)	Severe stenosis n (%)	Overall n (%)	p
CCA	19 (21.1)	13 (14.4)	58 (64.4)	90 (100.0)	-
PPV	-	-	-	78.9	-
AGE	65.95 ± 12.72	65.30 ± 11.20	66.55 ± 8.57	66.59 ± 9.86	0.91a
Body mass index					
Low weight	1 (14.3)	1 (14.3)	5 (71.4)	7 (100.0)	
Normal weight	7 (25.0)	5 (17.9)	16 (57.1)	28 (100.0)	
High weight	7 (18.9)	4 (10.8)	26 (70.3)	37 (100.0)	0.89b
Obesity I	2 (40.0)	2 (15.4)	9 (69.2)	13 (100.0)	
Obesity II	2 (40.0)	1 (10.0)	2 (40.0)	5 (100.0)	
Complications					
None	17 (18.9)	13 (15.1)	56 (65.1)	86 (100.0)	
Hypertension (220/110 mmHg)	1 (100.0)	0 (0.00)	0 (0.00)	1 (100.0)	
Complex ventricular arrhythmia	1 (100.0)	0 (0.00)	0 (0.00)	1 (100.0)	0.45b
Typical chest pain	0 (0.00)	0 (0.00)	1 (100.0)	1 (100.0)	
Arrhythmia and typical chest pain	0 (0.00)	0 (0.00)	1 (100.0)	1 (100.0)	
Arrhythmia type					
None	13 (21.7)	8 (13.3)	39 (65.0)	60 (100.0)	
SVES	0 (0.00)	2 (25.0)	6 (75.0)	8 (100.0)	0.65b
VES	6 (28.6)	3 (14.3)	12 (57.1)	21 (100.0)	
NSVT	0 (0.00)	0 (0.00)	1 (100.0)	1 (100.0)	
Medical procedure after CCA					
PTCA	-	-	34 (58.6)	-	
MRS	-	-	16 (27.6)	-	-
Pharmacological treatment	-	-	8 (13.8)	-	

Statistical methods: *a: one-way analysis of variance (ANOVA); b: Fisher's exact test.*
CCA: conventional coronary angiography; SVES: supraventricular extrasystole; VES: ventricular extrasystole; NSVT: non-sustained ventricular tachycardia; PPV: positive predictive value; PTCA: percutaneous transluminal coronary angioplasty; MRS: myocardial revascularization surgery.

stenosis. The PPV of the early-ECHO examination in women was 78.9%.

Only 4 patients (4.4%) had serious complications during the examination, determined as complex ventricular arrhythmias, hypertension (above 220/120 mmHg), or typical chest pain. It is also significant that 60 (66.7%) participants did not have arrhythmias during the examination, and from these 60, 39 (65%) had severe CAD. In the examinations of 58 patients with severe CAD, 06 (10.3%) had supraventricular extrasystole (SVES), 12 (20.7%) had ventricular extrasystole (VES), and 1 (1.7%) had non-sustained ventricular tachycardia (NSVT).

Regarding the medical conduct for patients with severe CAD, 34 (58.6%) underwent percutaneous transluminal coronary angioplasty; 16 (27.6%) underwent myocardial revascularization surgery; and 8 (13.8%) had their clinical treatment intensified.

The association between variables analyzed before and during the examination with a CAD predictor considering patients aged older than 60 years is shown in Table 2. Additionally, 25 (27.7%) participants aged < 59 years and 65 (72.2%) aged > 60 years were observed. It is noteworthy that women who were younger than 59 years old were more likely to have class 1 obesity (defined as a BMI between 30.0 and 34.9 kg/m^2), being represented by 8 patients (32.0%) with a statistically significant difference (p = 0.02) and adjusted residues (ra) of 3.1 confirming significance. Furthermore, when grouping overweight patients and those with grade 1 obesity, we observed that 70% of them presented severe CAD at CCA.

Another characteristic found during the examination was the lower need for high dobutamine doses in women over the age of 60 years. Nearly 81% of older patients reached the goal of the examination with a lower dose of dobutamine while 44% of younger patients (< 59 years) required a high dose of this medication, with a statistically significant difference (p = 0.01) and ra = 2.5 confirming the significance.

Discussion

Stress echocardiography is an established technique for assessing the extent and severity of CAD. The combination of echocardiography with physical, pharmacological, or electrical stress allows the detection of myocardial ischemia with excellent accuracy. This NIT provides diagnostic and prognostic accuracy that is similar to that of radionuclide stress perfusion imaging or magnetic resonance, but at a substantially lower cost and without environmental impact and hazards to the patient and physician.[17]

The present study demonstrated a low rate (4.4%) of relevant complications (defined as complex ventricular arrhythmias, arterial hypertension, and/or typical chest pain), which was different from the literature. Abreu *et al*. indicated an occurrence of typical chest pain in 53.8% of positive tests in octogenarians and complex arrhythmias, occurring in 6.4% of the examinations of patients aged 80 years or older. The frequency of extrasystoles varied between 27.6% in patients aged younger than 60 years and 47.8% in patients aged 80 years or older.[18] The finding rate of non-complex arrhythmias in patients with severe CAD was 10.3% for SVES and 20.7% for VES. The early use of isometric exercise in our early-ECHO protocol may have been a relevant factor for reducing test duration, as already demonstrated by Yao and colleagues,[8] thus leading to a lower rate of adverse events was observed.

Regarding the use of medications during the examination, a significant portion of older patients (> 60 years) did not require high dobutamine doses. This was shown by Secnus and Marwick in 1997, when they found that women had a higher heart rate than men both at rest and at the end of ECHO, in addition to the fact that fewer women needed atropine.[19] Abreu and colleagues also showed that octogenarians (mainly women) needed less medication during the exam, which may be due to less vagal activity and/or greater sensitivity to dobutamine in this population.[18]

Data showed that women aged 59 years and younger were more predisposed to having class 1 obesity. In the obese patient, the blood volume and capillary network are increased. In order to compensate for this, the cardiac output is increased according to the relation between excess weight and ideal weight. There is also an increase in oxygen consumption by the metabolism of adipose tissue, with most of the cardiac output destined to supply these cells. Moreover, the intensity of these changes is proportional to the time since the installation of this hemodynamic situation, and this pattern has been shown to be reversible with weight reduction.[20]

According to Herszkowicz et al.,[20] a population of obese women, without any clinical alterations or cardiovascular complications, showed a trend of higher values of systolic arterial pressure, myocardial mass, and left ventricular wall circumference stress, as well as a trend of early alterations of global diastolic function.[20]

Table 2 – Association between the outcome of patients aged 60 years or older and the variables analyzed before and during the examination (n=90)

Variables	Age ≤ 59 years old	Age ≥ 60 years old	n (%)	p
	n (%) (n = 25)	n (%) (n = 65)		
Body mass index				
Low weight	0 (0.0)	6 (9.2)	6 (6.7)	
Normal weight	5 (20.0)	24 (36.9)	29 (32.2)	
High weight	10 (40.0)	27 (41.5)	27 (10.0)	**0.02[b] ra=2.9**
Obesity I	8 (32.0)[ra]	5 (7.7)	13 (14.4)	
Obesity II	2 (8.0)	3 (4.6)	5 (5.6)	
Basal segment analysis				
Normal	18 (72.0)	54 (83.1)	72 (80.0)	0.25[b]
Dysfunction	7 (28.0)	11 (16.9)	18 (20.0)	
Low dose segment analysis				
Normal	13 (52.0)	37 (56.9)	50 (55.6)	0.81[a]
Dysfunction	12 (48.0)	28 (43.1)	40 (44.4)	
Use of high dose				
No	14 (56.0)	52 (80.0)[ra]	66 (73.3)	**0.03[a] ra=2.3**
Yes	11 (44.0)[ra]	13 (20.0)	24 (26.7)	
High dose segment analysis				
Normal	2 (18.2)	5 (38.5)	7 (29.2)	0.39[b]
Dysfunction	9 (81.8)	8 (61.5)	17 (70.8)	
Complications				
None	24 (96.0)	62 (95.4)	86 (95.6)	
Hypertension (220/110 mmHg)	1 (4.0)	0 (0.0)	1 (1.1)	
Complex ventricular arrhythmia	0 (0.0)	1 (1.5)	1 (1.1)	0.63[b]
Typical chest pain	0 (0.0)	1 (1.5)	1 (1.1)	
Arrhythmia and typical chest pain	0 (0.0)	1 (1.5)	1 (1.1)	
Arrhythmia type				
None	21 (84.0)	40 (61.5)	61 (67.8)	
SVES	2 (8.0)	6 (9.2)	8 (8.9)	0.15[b]
VES	2 (8.0)	18 (27.7)	22 (22.2)	
NSVT	0 (0.0)	1 (1.5)	1 (1.1)	
Medical procedure after CCA				
PTCA	7 (28.0)	27 (41.5)	34 (37.8)	
MRS	3 (12.0)	13 (20.0)	16 (17.8)	0.28[b]
Pharmacological treatment	2 (8.0)	6 (9.2)	8 (8.9)	

Statistical methods: *a: Pearson's chi-squared test; b: Fisher's exact test.*
SVES: supraventricular extrasystole; VES: ventricular extrasystole; NSVT: non-sustained ventricular tachycardia; CCA: conventional coronary angiography; PTCA: percutaneous transluminal coronary angioplasty; MRS: myocardial revascularization surgery.

Furthermore, the use of preventive measures against obesity in women, as well as the early identification of ventricular remodeling, has become an important factor in the fight against cardiovascular diseases in the female population.

In 2012, a comparative effectiveness review evaluated the diagnostic accuracy and risks of NIT in women with suspected symptoms of CAD. This review showed that ECHO provided a sensitivity of 79% and a specificity of 83% when compared with CCA.[21]

Our analyses showed that the PPV of early-ECHO in women was 78.9%. However, this analysis does not include the probability of pre-test CAD among patients, as well as the clinical aspects of thoracic pain presented by them. Pasierski et al.,[22] reported that, in hypertensive patients with angina, the specificity and PPV of exercise echocardiography were 96% and 97%. They also demonstrated that the advantage of stress echocardiography over the ECG stress test was more obvious in hypertensive women than in hypertensive men.[22]

Tong and Douglas reported the sensitivity and specificity of exercise echocardiography testing in women to be 91% and 80%, respectively. These data suggest that exercise echocardiography may be the diagnostic test of choice in women. From a cost-effectiveness point of view, these authors believe that most women should undergo exercise echocardiography as the initial diagnostic test, since its diagnostic accuracy is much higher than that of ECG stress testing.[23]

The prevalence of CAD in the studied population was 78.9%, and in cases of severe CAD (> 70% of stenosis), 27.6% of the patients underwent myocardial revascularization surgery; 58.6% underwent coronary angioplasty; and 13.8% received optimized clinical treatment. Heupler et al.,[24] demonstrated that exercise echocardiography provided incremental prognostic information over exercise ECG in populations with mixed genders or mixed pre-test CAD probability.[24] The incremental value of stress echocardiography over stress electrocardiography in a low-risk but mixed-gender population was demonstrated over 2 decades ago.[25]

Cortigiani et al.[26] found that echocardiographic evidence of ischemia on dobutamine or dipyridamole stress echocardiography was the only independent predictor of hard events in a group of 456 women who were not known to have CAD.[26] Supporting this analysis, Davar et al.[27] showed that positive stress echocardiography was the only independent predictor of future cardiac events, with a relative risk of 8.9 (95% confidence interval 1.0 to 76.5, p = 0.04). The cumulative event-free survival rate 38 months after stress echocardiography was 98.8% for patients with negative stress echocardiography results and 50.7% for patients with positive results.[27]

Moreover, in an earlier study, exercise echocardiography was found to be the optimal method of diagnosing CAD in women.[28] Recommendations from the European Society of Cardiology suggest the preferential use of non-ionizing imaging techniques in highly vulnerable patients such as younger women.[29]

Conclusions

Early-ECHO is a test with a low complication rate that shows a high PPV for the diagnosis of myocardial ischemia in women, providing fast identification of this disease with early treatment of injuries and preventing potential major complications and/or death due to CAD.

Finally, more studies should be conducted in order to recommend the early-ECHO protocol as a NIT in the assessment of CAD in women.

Author contributions

Acquisition of data: Fischer Bacca CO, Lindner IA, Oliveira, PS. Analysis and interpretation of the data: Lindner IA, Rocha, FR, Matsuda JB. Statistical analysis: Lindner, IA, Rocha, FR. Writing of the manuscript: Fischer Bacca CO, Lindner IA, Oliveira PS, Rocha, FR, Bacca LE. Critical revision of the manuscript for intellectual content: Visentainer, J.

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 UNIDAVI (*Centro Universitário para o Desenvolvimento do Alto Vale do Itajaí*) under the protocol number CAEE: 9103718 8 0000 5676. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Brasil. Ministério da Saúde. Banco de dados do Sistema Único de Saúde – DATASUS [Internet]. Brasília (DF); 2020 [Cited 2020 Dec 21]. Available from: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sim/cnv/obt10uf.def..
2. Mieres JH, Shaw LJ, Arai A, Budoff MJ, Flamm SD, Hundley WG, et al. Role of noninvasive testing in the clinical evaluation of women with suspected coronary artery disease: consensus statement from the Cardiac Imaging Committee, Council on Clinical Cardiology, and the Cardiovascular Imaging and Intervention Committee, Council on Cardiovascular Radiology and Intervention, American Heart Association. Circulation. 2005;111(5):682-96. doi: 10.1161/01.CIR.0000155233.67287.60.
3. Moreira MCV, Montenegro ST, Paola AAV, editors. Livro-texto da Sociedade Brasileira de Cardiologia. 2nd ed. Barueri: Manole; 2015.
4. Camarozano AC, Weitzel LH. Ecocardiografia de estresse e contraste. 2nd ed. Rio de Janeiro: Revinter; 2013.
5. Camarozano AC, Siqueira-Filho AG, Weitzel LH, Resende P, Noé RA. The effects of early administration of atropine during dobutamine stress echocardiography: advantages and disadvantages of early dobutamine-atropine protocol. Cardiovasc Ultrasound. 2006;4:17. doi: 10.1186/1476-7120-4-17.
6. Lewandowski TJ, Armstrong WF, Bach DS. Reduced test time by early identification of patients requiring atropine during dobutamine stress echocardiography. J Am Soc Echocardiogr. 1998;11(3):236-42. doi: 10.1016/s0894-7317(98)70085-9.
7. Tsutsui JM, Osório AF, Lario FA, Fernandes DR, Sodre G, Andrade JL, et al. Comparison of safety and efficacy of the early injection of atropine during dobutamine stress echocardiography with the conventional protocol. Am J Cardiol. 2004;94(11):1367-72. doi: 10.1016/j.amjcard.2004.07.141.
8. Yao SS, Moldenhauer S, Sherrid MV. Isometric handgrip exercise during dobutamine-atropine stress echocardiography increases heart rate acceleration and decreases study duration and dobutamine and atropine dosage. Clin Cardiol. 2003;26(5):238-42. doi: 10.1002/clc.4960260509.
9. Dattilo G, Patanè S, Zito C, Lamari A, Tulino D, Marte F, et al. Handgrip exercise associated with dobutamine stress echocardiography. Int J Cardiol. 2010;143(3):298-301. doi: 10.1016/j.ijcard.2009.03.016.
10. Khan IA, Otero FJ, Font-Cordoba J, McCulloch M, Sheahan RG, Parmar R, et al. Adjunctive handgrip during dobutamine stress echocardiography: invasive assessment of myocardial oxygen consumption in humans. Clin Cardiol. 2005;28(7):349-52. doi: 10.1002/clc.4960280709.
11. Katritsis DG, Korovesis S, Karvouni E, Giazitzoglou E, Karabinos I, Tzanalaridou E, et al. Handgrip-enhanced myocardial fractional flow reserve for assessment of coronary artery stenoses. Am Heart J. 2006;151(5):1107.e1-7. doi: 10.1016/j.ahj.2005.09.023.
12. Pellikka PA, Arruda-Olson A, Chaudhry FA, Chen MH, Marshall JE, Porter TR, et al. Guidelines for performance, interpretation, and application of stress echocardiography in ischemic heart disease: from the American Society of Echocardiography. J Am Soc Echocardiogr. 2020;33(1):1-41.e8. doi: 10.1016/j.echo.2019.07.001.
13. Pijls NH, Sels JW. Functional measurement of coronary stenosis. J Am Coll Cardiol. 2012;59(12):1045-57. doi: 10.1016/j.jacc.2011.09.077.
14. Scanlon PJ, Faxon DP, Audet AM, Carabello B, Dehmer GJ, Eagle KA, et al. ACC/AHA Guidelines for Coronary Angiography: executive summary and recommendations. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Coronary Angiography) developed in collaboration with the Society for Cardiac Angiography and Interventions. Circulation. 1999;99(17):2345-57. doi: 10.1161/01.cir.99.17.2345.
15. Dehmer GJ, Weaver D, Roe MT, Milford-Beland S, Fitzgerald S, Hermann A, et al. A contemporary view of diagnostic cardiac catheterization and percutaneous coronary intervention in the United States: a report from the CathPCI Registry of the National Cardiovascular Data Registry, 2010 through June 2011. J Am Coll Cardiol. 2012;60(20):2017-31. doi: 10.1016/j.jacc.2012.08.966.
16. Fihn SD, Blankenship JC, Alexander KP, Bittl JA, Byrne JG, Fletcher BJ, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. J Thorac Cardiovasc Surg. 2015;149(3):e5-23. doi: 10.1016/j.jtcvs.2014.11.002.
17. Sicari R, Cortigiani L. The clinical use of stress echocardiography in ischemic heart disease. Cardiovasc Ultrasound. 2017;15(1):7. doi: 10.1186/s12947-017-0099-2.
18. Abreu JS, Diógenes TC, Farias AG, Morais JM, Paes JN Jr. Safety and feasibility of dobutamine-atropine stress echocardiography in octogenarian patients. Arq Bras Cardiol. 2005;85(3):198-204. doi: 10.1590/s0066-782x2005001600009.
19. Secknus MA, Marwick TH. Influence of gender on physiologic response and accuracy of dobutamine echocardiography. Am J Cardiol. 1997;80(6):721-4. doi: 10.1016/s0002-9149(97)00502-x.
20. Herszkowicz N, Barbato A, Salvi W, Pinheiro D, Pantaleão D, Halpern A, et al. Contribution of Doppler echocardiography to the evaluation of systolic and diastolic function of obese women versus a control group. Arq Bras Cardiol. 2001;76(3):189-96. doi: 10.1590/s0066-782x2001000300002.
21. Dolor RJ, Patel MR, Melloni C, Chatterjee R, McBroom AJ, Musty MD, et al. Noninvasive technologies for the diagnosis of coronary artery disease in women. Rockville (MD): Agency for Healthcare Research and Quality (US); 2012.
22. Pasierski T, Szwed H, Malczewska B, Firek B, Kośmicki M, Rewicki M, et al. Advantages of exercise echocardiography in comparison to dobutamine echocardiography in the diagnosis of coronary artery disease in hypertensive subjects. J Hum Hypertens. 2001;15(11):805-9. doi: 10.1038/sj.jhh.1001265.
23. Tong AT, Douglas PS. Stress echocardiography in women. Cardiol Clin. 1999;17(3):573-82. doi: 10.1016/s0733-8651(05)70097-7.
24. Heupler S, Mehta R, Lobo A, Leung D, Marwick TH. Prognostic implications of exercise echocardiography in women with known or suspected coronary artery disease. J Am Coll Cardiol. 1997;30(2):414-20. doi: 10.1016/s0735-1097(97)00167-8.
25. Colon PJ 3rd, Mobarek SK, Milani RV, Lavie CJ, Cassidy MM, Murgo JP, et al. Prognostic value of stress echocardiography in the evaluation of atypical chest pain patients without known coronary artery disease. Am J Cardiol. 1998;81(5):545-51. doi: 10.1016/s0002-9149(97)00987-9.
26. Cortigiani L, Dodi C, Paolini EA, Bernardi D, Bruno G, Nannini E. Prognostic value of pharmacological stress echocardiography in women

with chest pain and unknown coronary artery disease. J Am Coll Cardiol. 1998;32(7):1975-81. doi: 10.1016/s0735-1097(98)00477-x.

27. Davar JI, Roberts EB, Coghlan JG, Evans TR, Lipkin DP. Prognostic value of stress echocardiography in women with high (> or = 80%) probability of coronary artery disease. Postgrad Med J. 2001;77(911):573-7. doi: 10.1136/pmj.77.911.573

28. Marwick TH, Anderson T, Williams MJ, Haluska B, Melin JA, Pashkow F, et al. Exercise echocardiography is an accurate and cost-efficient technique for detection of coronary artery disease in women. J Am Coll Cardiol. 1995;26(2):335-41. doi: 10.1016/0735-1097(95)80004-z.

29. Kristensen SD, Knuuti J, Saraste A, Anker S, Bøtker HE, Hert SD, et al. 2014 ESC/ESA Guidelines on non-cardiac surgery: cardiovascular assessment and management: The Joint Task Force on non-cardiac surgery: cardiovascular assessment and management of the European Society of Cardiology (ESC) and the European Society of Anaesthesiology (ESA). Eur Heart J. 2014;35(35):2383-431. doi: 10.1093/eurheartj/ehu282.

Int J Cardiovasc Sci. 2021; 34(4):452-458

ORIGINAL ARTICLE

The REBECGA Brazilian Registry of Pregnancy and Heart Disease: Rationale and Design

Walkiria Samuel Avila,[1] Maria Alayde Mendonça Rivera,[2,3] Celi Marques-Santos,[3] Ivan Romero Rivera,[2] Maria Elizabeth Navegantes Caetano Costa,[4] Alexandre Jorge Gomes de Lucena,[5] Claudia Maria Vilas Freire,[6] Regina Coeli Marques de Carvalho,[7,8] Daniel Born,[9] Felipe Favorette Campanharo,[9] Fabio Bruno Silva[10]

Instituto do Coração da Faculdade de Medicina da Universidade de São Paulo (InCor-FMUSP),[1] São Paulo, SP – Brazil
Hospital Universitário da Universidade Federal de Alagoas,[2] Maceió, AL – Brazil
Santa Casa de Misericordia de Maceió,[3] Maceió, AL – Brazil
Universidade Tiradentes,[3] Aracaju, SE – Brazil
Fundação Pública Estadual Hospital de Clínicas Gaspar Viana,[4] Belém, PA – Brazil
Hospital Agamenon Magalhães,[5] Recife, PE – Brazil
Hospital das Clinicas da Universidade Federal de Minas Gerais,[6] Belo Horizonte, MG – Brazil
Hospital Geral de Fortaleza,[7] Fortaleza, CE – Brazil
Secretaria de Saúde do Estado do Ceará (SESA),[8] Fortaleza, CE – Brazil
Hospital São Paulo - Universidade Federal de São Paulo,[9] São Paulo, SP – Brazil
Instituto Dante Pazzanese de Cardiologia,[10] São Paulo, SP – Brazil

Abstract

Background: Maternal mortality rates in Brazil remain above the goals established by the United Nations Sustainable Development Goals. Heart disease is estimated to affect 4% of all pregnancies and remains by itself the main indirect obstetric cause of maternal death. In the last decades, a significant improvement in the prognosis of heart diseases has made pregnancy possible in women with heart disease and provided better maternal and fetal outcomes.

Objectives: To establish a multicenter Brazilian Registry of pregnant women with heart disease; to study the causes of immediate and late maternal mortality; and to assess the prevalence of heart disease in the country's macro-regions.

Methods: This is an observational study, with retrospective and prospective stages, of the clinical and obstetric progression of pregnant women with heart disease. These women consecutively received care during pregnancy and will be followed up for up to a year after delivery at public and private hospitals with infrastructure for the execution of this project, a principal investigator, and approval by Ethics and Research Committees.

Results: Our results will be presented after data collection and statistical analysis, aiming to demonstrate immediate and late maternal mortality rates, as well as the prevalence of heart disease in the country and its cardiovascular and obstetric complications during pregnancy.

Conclusions: REBECGA will be the Brazilian Registry of heart disease and pregnancy and it will contribute to planning preventive measures, raising financial resources for the improvement of high-risk prenatal care, and reducing immediate and late maternal mortality due to heart disease.

Keywords: Pregnancy; Heart Diseases; Maternal Mortality; Cardiovascular Pregnancy Complications.

Introduction

Maternal mortality is a severe social problem in Brazil, reflecting our condition as an emerging country. Assistance to high-risk pregnant women displays

Walkiria Samuel Avila, MD, PhD
Coordinator of the Heart Disease and Pregnancy and Reproductive Counseling Program at InCor-HCFMUSP
Hospital das Clínicas, Faculty of Medicine, University of São Paulo

Mailing Address: Maria Alayde Rivera
Av. Lourival Melo Mota, s/n. Postal Code: 57072-900, Tabuleiro do Martins, Maceió, AL – Brazil.
E-mail: malayde1@uol.com.br

DOI: https://doi.org/10.36660/ijcs.20200419

Manuscript received December 31, 2020; revised manuscript March 13, 2021; accepted June 02, 2021.

profound differences, specifically considering those with heart disease and the proportion of avoidable deaths, in the various regions of Brazil.[1]

In the last 3 decades, Brazil reported a marked reduction in maternal mortality rate — from 143.2 to 64 deaths per 100 000 live births. However, these coefficients are higher than those established by the United Nations Sustainable Development Goals and 6 times higher than those accepted by the World Health Organization.[2]

Heart disease is the main indirect obstetric cause of maternal death, being present in 4% of pregnancies. The impact of heart disease in maternal mortality was investigated in 27 referral obstetric units, and maternal death showed a prevalence ratio that was 4 times higher (4.8 vs 1.2) in pregnant women with heart disease.[3]

In Brazil, rheumatic disease contributes to an expressive incidence of acquired heart disease in young women, with a 4 times higher prevalence ratio when compared to developed countries. The growing population of pregnant women with congenital heart disease and cardiomyopathies has also contributed to significant complication and maternal mortality rates during pregnancy.[4]

In the last decades, a significant improvement in the prognosis of cardiovascular diseases and a higher life expectancy for children and adolescents with heart disease has been observed, including the safe development of pregnancy. However, the country lacks national data on these changes.

Worldwide multicenter registries, guidelines, and positions have been established with the commitment of reducing maternal mortality due to heart disease.[5-9] In clinical practice, the applicability of maternal cardiovascular risk scores published in the international literature faces serious limitations, especially because the epidemiology of heart diseases in reproductive age and the social and demographic characteristics of the Brazilian population are very diverse.

In agreement with the current global movement, the elaboration of the Brazilian Registry of Pregnancy and Heart Diseases, led by the Women's Cardiology Department (DCM) and hereinafter named the REBECGA Registry, responds to our social responsibility regarding the quality of life of women with heart disease. Notably, it contributes to planning preventive measures, raising financial resources for providing better prenatal care, and reducing immediate and late maternal mortality due to heart diseases manifested during pregnancy.

The primary objective of the REBECGA Registry is the construction of a national register of heart diseases manifested during pregnancy, focusing on the study of immediate and late maternal mortality due to heart disease. Our secondary objectives are the identification of the cardiovascular complications of pregnancy and the prevalence of these heart diseases in the country's macro-regions.

Methods

This is an observational study with a retrospective (cross-sectional) stage and a prospective (longitudinal) stage, including women with heart disease who consecutively received care during pregnancy and were followed up for up to a year after delivery. We will analyze pre-selected maternal, obstetric, and fetal variables in both stages of the registry (Chart 1). Data from the retrospective stage, which ranged from 2017 to 2020, will be obtained through the analysis of medical records and or/telephone contact; as for the prospective stage (from 2021 to 2026), they will be collected at in-person periodical visits through paper forms and further storage on an online platform. During the prospective stage, clinical and obstetric approaches should follow the recommendations by the Brazilian Society of Cardiology (SBC) Statement for Management of Pregnancy and Family Planning in Women with Heart Disease – 2020 in order to reduce discrepancies in results.

All participants of the registry or their legal representatives must sign the free and informed consent form (FICF). In case the patient has not reached legal age, the FICF shall be signed by her legal guardian. Patients who do not attend scheduled visits after delivery will be interviewed by telephone for collecting obstetric and perinatal information. We have not anticipated complementary examinations. The participant hospitals, whether public or private, should present: 1) approval of the project by the Research and Ethics Committee of the participating institution; 2) infrastructure for executing the project; 3) a principal investigator who will be responsible for the Registry until the end of the project.

Inclusion and exclusion criteria: We will include pregnant women with heart disease, with anatomical and etiological diagnosis defined at the first prenatal consult, regardless of their involvement in other clinical studies, after signing of the FICF. Structural and electrical heart diseases, as well as complicating factors included in the Registry platform, are presented on Charts 2 and 3, respectively.

Chart 1 – Variables included in the registry
Patient identification: record number, age, date of birth, gestational age at first consult;
Characterization of heart disease: anatomical and etiological diagnosis, previous cardiovascular intervention (type and time/years), complicating factors, associated structural heart injury;
Obstetric history: number of pregnancies, deliveries, and miscarriages;
Clinical characteristics: New York Heart Association (NYHA) functional classification at first prenatal consult;
Comorbidities: chronic arterial hypertension, bronchial asthma, gestational diabetes, thyroid disorders, obesity (body mass index [BMI] > 30 Kg/m^2);
Electrocardiographic variables (12-lead recording);
Echocardiographic variables (two-dimensional transthoracic echocardiography)
Cardiac biomarkers: natriuretic peptide (BNP), troponin, international normalized ratio (INR), anti-factor Xa, others;
Cardiovascular complications during pregnancy;
Pharmacological intervention
Anticoagulation – Use in the first, second, and third trimester, as well as on the seventh, 14th, and 42nd day after delivery. Anticoagulants considered for the registry: low molecular weight heparin, unfractionated heparin, warfarin;
Non-pharmacological intervention, considering percutaneous intervention or heart surgery performed during pregnancy or puerperium;
Type and date of delivery, gestational age at delivery (in weeks);
Type of anesthesia used during delivery;
Neonatal complications related to maternal heart disease (congenital malformations or consequences of medications used during pregnancy);
Cardiovascular complications during delivery and puerperium;
Obstetric complications of pregnancy, delivery, and puerperium;
Hospitalization for treating cardiovascular complications during pregnancy or puerperium;
Late maternal death: considering 12 months after delivery.

Chart 2 – Heart disease diagnosis	
Valvular heart disease	Congenital heart disease
Cardiomyopathies	Pericardial disease
Aortic diseases	Ischemic heart disease
Inflammatory or infiltrative heart disease	
Cardiac arrhythmia with intervention indication	

Chart 3 – Complicating factors	
Ventricular dysfunction	Fibrillation/atrial flutter
Pulmonary hypertension	Hypoxemia
Residual injury in the late postoperative period	
Graft or prosthesis dysfunction	

Chart 4 – Maternal cardiac complications	
Heart failure	Acute pulmonary edema
Cardiac syncope	Acute myocardial infarction
Aortic dissection	Infective endocarditis
Arterial or venous thromboembolism	
Need for anticoagulants	
Cardiorespiratory arrest	
Non-pharmacological intervention	

Chart 5 – Pharmacological treatment during pregnancy	
Loop diuretics	Beta-blockers
Calcium channel blockers	Antiarrhythmics
Vasodilators	Anticoagulants
Platelet antiaggregants	Others

Women to be excluded from the study are 1) patients with severe diseases (renal, hepatic, lymphatic, neoplasms, and others); 2) patients with conditions that interfere in their participation or capacity of concluding the study; 3) those who did not present structural or electrical heart disease. The studied variables will include clinical, obstetric, and fetal complications, as well as pharmacological and interventional management during pregnancy (Charts 4 and 5).

Results of the 12-lead electrocardiography and the two-dimensional transthoracic echocardiography will be analyzed, and echocardiographic results related to the structural cardiac injury will be considered. For example, the echocardiographic data obtained for valvular heart disease will not be the same as those for congenital heart disease or cardiomyopathies, and so on. Cardiac biomarkers will only be considered in case of acute cardiac events occurring during pregnancy.

Data recording

Variables selected in this study (Charts 1–6) for each patient will be stored in the Research Electronic Data Capture (REDCap) platform, individually and consecutively, in a specific form dedicated to this registry (Table 1). Professionals responsible for collecting and storing data in the various participant centers will undergo initial online training for guaranteeing quality in data collection. The principal investigator in each center will be responsible for consecutively recording data obtained on the selected patients.

Expected outcomes

Primary: immediate and late mortality rates due to heart disease;

Secondary: cardiac, obstetric, and fetal complications and need for pharmacological or non-pharmacological intervention related to heart diseases.

Data management and quality assurance

The REDCap platform was chosen because Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP) has the software license and thus no additional costs with data management would be generated for the project. In each participating center, the team will fill out an electronic form at the REDCap platform. Data management in the REBECGA registry will include the following steps: 1) a REDCap coordinating team will undergo training sessions before the beginning of the study for guaranteeing consistency throughout the project's procedures, including data collection and report generation; 2) participating institutions will receive an Operations Manual with the

Table 1 – Variables selected for inclusion in the REBECGA Registry *Research Electronic Data Capture* (*REDCap*)

1)	Patient identification: record number, age, date of birth, gestational age at first consult;
2)	Characterization of heart disease: anatomical and etiological diagnosis, previous cardiovascular intervention (type and time/years), complicating factors, associated structural heart injury;
3)	Obstetric history: number of pregnancies, deliveries, and miscarriages;
4)	Clinical characteristics: New York Heart Association (NYHA) functional classification at first prenatal consult;
5)	Comorbidities: chronic arterial hypertension, bronchial asthma, gestational diabetes, thyroid disorders, obesity (body mass index [BMI] > 30 Kg/m^2);
6)	Electrocardiographic variables;
7)	Echocardiographic variables (two-dimensional transthoracic echocardiography)
8)	Cardiac biomarkers: natriuretic peptide (BNP), troponin, international normalized ratio (INR), anti-factor Xa, others;
9)	Cardiovascular complications during pregnancy;
10)	Pharmacological intervention considering the class of medications with cardiovascular action;
11)	Anticoagulation – Use in the first, second, and third trimester, as well as on the seventh, 14th, and 42nd day after delivery. Anticoagulants considered for the registry: low molecular weight heparin, unfractionated heparin, warfarin;
12)	Non-pharmacological intervention, considering percutaneous intervention or heart surgery performed during pregnancy or puerperium;
13)	Type and date of delivery, gestational age at delivery (in weeks);
14)	Type of anesthesia used during delivery;
15)	Neonatal complications related to maternal heart disease (congenital malformations or consequences of medications used during pregnancy);
16)	Cardiovascular complications during delivery and puerperium;
17)	Obstetric complications of pregnancy, delivery, and puerperium;
18)	Hospitalization for treating cardiovascular complications during pregnancy or puerperium;
19)	Late maternal death: considering time after delivery in months, cardiac and obstetric causes, or others.

description of each step of the protocol and will have telephonic support for solving problems or doubts; 3) the Academic Research Organization (ARO) of the project's coordinating center will analyze monthly reports, rates of events, and cardiac outcomes; 4) the database centralized at the coordinating center will perform internal verifications of validity and variation for identifying errors or omissions and notifying the participating institutions; 5) in the prospective stage, we will accept a loss to follow-up of up to 5%; 6) the coordinating team will perform an inspection at institutions with monitoring purposes, if necessary.

Project management

The study will have an investigating committee constituted by members of the DCM of the SBC, being responsible for selecting participating centers and managing the data registry platform. In each center, the principal investigator is committed to selecting patients, managing incomplete data, storing data on the REDCap platform, and participating in periodical meetings with the management committee for decision-making regarding the progress of the study.

Sample size

We will perform 3 intermediate analyses throughout the study: 1) the retrospective stage, corresponding to the period between 2017 and 2020; 2) the prospective stage – phase 1, which corresponds to the period between 2021 and 2023; and 3) the prospective stage – final phase, between 2024 and 2026. In the retrospective stage, we will use convenience sampling including pregnant women who consecutively received care between 2017 and 2020. In the prospective stage, our sample calculation estimates 300 to 350 women/year, which corresponds to a mean number of 40 to 70 women/year to receive care at the participating institutions.

Statistical analysis

The normality of data distributions will be verified through a Shapiro-Wilk test, with a significance level of 5%, in addition to a graphical analysis by gg-plot and histograms. Continuous variables with normal distribution will be presented as means and standard deviations, while those with non-normal distributions will be presented as absolute and relative frequencies, with the respective confidence intervals. For determining the association between categorical variables, we will use the chi-squared test where the odds ratio will be established for dependent variables with a significance level of 5% and a 95% confidence interval. For quantitative variables, Pearson's correlation coefficient will be employed for determining the correlation between variables, based on the same significance level. Estimates for quantitative variables with normal distribution will use the unpaired Student's t-test with a 5% significance level. Non-parametric variables, if dependent, will be compared via a Wilcoxon test; if independent, the Mann-Whitney test will be employed for statistical inference. All analyses will be performed using R software, version 4.0.5.

Ethical aspects

This study was approved by the Ethics and Research Committee of HC-FMUSP – Protocol No. SDC5232/21/007 – and will be conducted according to the current Brazilian legislation on research ethics, including Resolutions 466/2012 – CNS-CONEP and 510/2016 – CNS. This clearance allows each participating center to submit a protocol to local committees. Eventual amendments to the protocol will also require approval by the ethics committees, if applicable, according to local laws and regulations.

Confidentiality regarding the study data will be guaranteed by the safe electronic retransmission to the coordinating center, with strictly confidential data storage and maintenance according to the current legislation. Participants will not be identified at any time.

The study will be conducted by the Clinical Research Projects Committee of the DCM of the SBC, and its content is intellectual property of this committee; the use of the study data for other ends that not the REBECGA Registry is thus considered illegal.

Result publication

Publications related directly to the main results of the REBECGA Registry will be produced with group authorship and the roles of all investigators will be recognized in an appendix and under the responsibility of the Registry's Investigating Committee. Subsequent publications will be authored by specific individuals, representing investigators of the REBECGA Registry. The selection of professionals for leading the writing of these subsequent publications by the Registry's Investigating Committee will depend on their roles and contributions to the study, as well as on their interests and scientific knowledge. Data will be published after conclusion of the 3 stages and will be available in the DCM at the SBC website.

Coordinating center: Project Management Unit of Instituto do Coração (InCor), HC-FMUSP, Rua Dr Enéas Carvalho de Aguiar, No. 44, Cerqueira César – SP. Postal Code: 05403-000.

Funding

The REBECGA registry is property of the DCM in partnership with the SBC and will use financial resources allocated to its execution. Resources will be raised with the support of the SBC and Research Support Foundations (FAPs) of each state involved in the study. The project will be submitted to PROADS, CNPq and CAPES after their respective calls for proposals.

Study limitations

In the retrospective stage, data loss could happen when considering that no uniform protocol was adopted beforehand. In the prospective stage, there will be no control group since this is an observational study. Resource inequalities, the fact that the maternity ward is located near the cardiology center, and differences in the number of patients in each center will be considered in the statistical analysis. At this moment, the South region does not have a representing institution fulfilling the criteria established by our methodology.

Acknowledgments

Iris Tikkanen Belitsky, graduate student in Bioinformatics at the Inter-unit Graduate Program in Bioinformatics of Universidade de São Paulo (IME-USP), for her consultancy in our statistical analysis.

Member of the Investigating Committee and president of the DCM (biennium 2020–2021) of the SBC Dr. Celi Marques Santos.

Participating institutions – principal investigators

InCor-FMUSP – **Prof. Dr. Walkiria Samuel Avila**; Hospital Geral de Fortaleza – Secretaria de Saúde do Estado do Ceará (SESA) – **Dr. Regina Coeli Marques de Carvalho**; Hospital das Clínicas da Universidade Federal de Minas Gerais – **Dr. Claudia Maria Vilas Freire**; Instituto Dante Pazzanese de Cardiologia – **Dr. Fabio Bruno Silva**; Hospital Universitário da Universidade Federal de Alagoas – **Dr. Maria Alayde Mendonça Rivera** and **Dr. Ivan Romero Rivera**; Hospital Agamenon Magalhães – **Dr. Alexandre Jorge Gomes de Lucena**; Hospital São Paulo – Universidade Federal de São Paulo – Escola Paulista de Medicina – **Dr. Felipe Favorette Campanharo** and **Dr. Daniel Born**; Fundação Pública Estadual Hospital de Clínicas Gaspar Viana – Secretaria de Saúde do Estado do Pará; **Dr. Elizabeth Caetano**.

Author contributions

Conception and design of the research: Avila WS, Rivera MAM, Marques-Santos C, Rivera IR, Costa MENC, Lucena AJG, Freire CMV, Carvalho RCM, Born D, Campanharo FF, Silva FB. Acquisition of data: Avila WS, Rivera MAM, Marques-Santos C, Rivera IR, Costa MENC, Lucena AJG, Freire CMV, Carvalho RCM, Born D, Campanharo FF, Silva FB. Analysis and interpretation of the data: Avila WS, Rivera MAM, Marques-Santos C, Rivera IR, Costa MENC, Lucena AJG, Freire CMV, Carvalho RCM, Born D, Campanharo FF, Silva FB. Statistical analysis: Avila WS, Rivera MAM, Marques-Santos C, Rivera IR, Costa MENC, Lucena AJG, Freire CMV, Carvalho RCM, Born D, Campanharo FF, Silva FB. Obtaining financing: Avila WS, Rivera MAM, Marques-Santos C, Rivera IR, Costa MENC, Lucena AJG, Freire CMV, Carvalho RCM, Born D, Campanharo FF, Silva FB. Writing of the manuscript: Avila WS, Rivera MAM, Marques-Santos C, Rivera IR, Costa MENC, Lucena AJG, Freire CMV, Carvalho RCM, Born D, Campanharo FF, Silva FB. Critical revision of the manuscript for intellectual content: Avila WS, Rivera MAM, Marques-Santos C, Rivera IR, Costa MENC, Lucena AJG, Freire CMV, Carvalho RCM, Born D, Campanharo FF, Silva FB.

Potential Conflict of Interest

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

Sources of Funding

This study was partially funded by *Sociedade Brasileira de Cardiologia* and *Fundação de Pesquisa da USP*.

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 USP - *Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo* – HCFMUSP under the protocol number 42739321.9.1001.0068. 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. Carvalho PI, Frias PG, Lemos MLC, Frutuoso LALM, Figueirôa BQ, Pereira CCB, et al. Sociodemographic and Health Care profile of Maternal Death in Recife, PE, Brazil, 2006-2017: A Descriptive Study. Epidemiol Serv Saude. 2020;29(1):e2019185. doi: 10.5123/S1679-49742020000100005.
2. Brasil. Ministério da Saúde. Secretaria de Vigilância em Sáude. Boletim Epidemiológico;2020;51(51):1-33
3. Campanharo FF, Cecatti JG, Haddad SM, Parpinelli MA, Born D, Costa ML, et al. The Impact of Cardiac Diseases during Pregnancy on Severe Maternal Morbidity and Mortality in Brazil. PLoS One. 2015;10(12):e0144385. doi: 10.1371/journal.pone.0144385.
4. Avila WS, Rossi EG, Ramires JA, Grinberg M, Bortolotto MR, Zugaib M, et al. Pregnancy in Patients with Heart Disease: Experience with 1,000 Cases. Clin Cardiol. 2003;26(3):135-42. doi: 10.1002/clc.4960260308.
5. Silversides CK, Grewal J, Mason J, Sermer M, Kiess M, Rychel V, et al. Pregnancy Outcomes in Women with Heart Disease: The CARPREG II Study. J Am Coll Cardiol. 2018;71(21):2419-30. doi: 10.1016/j.jacc.2018.02.076.
6. Roos-Hesselink J, Baris L, Johnson M, Backer J, Otto C, Marelli A, et al. Pregnancy Outcomes in Women with Cardiovascular Disease: Evolving Trends Over 10 Years in the ESC Registry of Pregnancy and Cardiac disease (ROPAC). Eur Heart J. 2019;40(47):3848-55. doi: 10.1093/eurheartj/ehz136.
7. Balci A, Sollie-Szarynska KM, van der Bijl AG, Ruys TP, Mulder BJ, Roos-Hesselink JW, et al. Prospective Validation and Assessment of Cardiovascular and Offspring Risk Models for Pregnant Women with Congenital Heart Disease. Heart. 2014;100(17):1373-81. doi: 10.1136/heartjnl-2014-305597.
8. Pijuan-Domènech A, Galian L, Goya M, Casellas M, Merced C, Ferreira-Gonzalez I, et al. Cardiac Complications During Pregnancy are Better Predicted With the Modified WHO Risk Score. Int J Cardiol. 2015;195:149-54. doi: 10.1016/j.ijcard.2015.05.076
9. Avila WS, Alexandre ERG, Castro ML, Lucena AJG, Marques-Santos C, Freire CMV, et al. Brazilian Cardiology Society Statement for Management of Pregnancy and Family Planning in Women with Heart Disease - 2020. Arq Bras Cardiol. 2020;114(5):849-942. doi: 10.36660/abc.20200406.

EDITORIAL

REBECGA Registry: A Multicenter Study for the Reduction of Maternal Mortality Due to Heart Diseases Manifested During Pregnancy

Karyne Pollo de Souza and Christianne Brêtas Vieira Scaramello

Universidade Federal Fluminense - Instituto Biomédico, Niterói, RJ – Brazil

Editorial referring to the article: The REBECGA Brazilian Registry of Pregnancy and Heart Disease: Rationale and Design

According to the literature, although the prevalence of heart disease in pregnancy varies considerably among countries, cardiovascular disease is responsible for 1% to 4% of complicated pregnancies in industrialized countries. This pattern is related to cardiovascular risk factors, such as smoking, diabetes, obesity, and hypertension, especially in low- and middle-income countries, as well as late motherhood and the presence of congenital heart disease, mainly in high-income countries.[1,2]

Improved diagnostic methods and therapeutic alternatives have encouraged maternity by promoting safer pregnancies. However, heart disease is still the leading non-obstetric cause of maternal mortality worldwide. Although the rate of maternal mortality has decreased in Brazil over the last three decades, it continues to be higher than estimated for this millennium.[3]

As noticed throughout the world, the percentage of congenital heart disease during pregnancy has risen in Brazil over the past 50 years due to improved surgical and late postoperative treatment that allowed an increased number of children with congenital heart disease to reach childbearing age. The well-accepted World Health Organization classification of the risk stratification model for pregnancy in patients with congenital heart disease considers this condition as risk III, meaning medical advice against pregnancy.[4]

Pregnancy leads to intrinsic hormonal stimulation in the organism and physiological changes of the cardiovascular system, which are necessary for adequate pregnancy development. The consequent hemodynamic overload may reveal previous heart diseases or aggravate the functional state of underlying heart disease. Thus, it may increase the risk of adverse maternal cardiac, obstetric, fetal, and neonatal outcomes.[5]

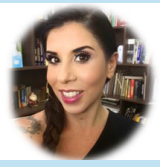
The quality of healthcare provided to women during prenatal care reflects the population's living conditions, and a country's maternal mortality rate is one of the most sensitive indicators.[3] The coexistence of cardiac disease and pregnancy presents challenges across the spectrum of prevention, diagnosis, treatment, and health service delivery that are unique for both mother and baby.[5]

In this context, the proposal of Avila et al.[6], encompassing the development of a multicenter Brazilian registry of pregnant women with heart disease (REBECGA Registry) with the aim of contributing to planning preventive measures, fundraising for improvement of prenatal care for high-risk pregnancies, and reducing immediate and late maternal mortality due to heart disease is beyond interesting; it is necessary.

Avila et al.[6] intend to study the causes of immediate and late maternal mortality, ascertaining the prevalence of heart disease in the country's macroregions. To achieve this purpose, they will conduct an observational study, encompassing retrospective (data from medical records between 2017 and 2020) and prospective (data from face-to-face consultations between 2020 and 2026) analysis of clinical and obstetric evolution of pregnant women with heart disease, with one year of follow-up after delivery.

Keywords

Heart Diseases; Pregnant Women; Maternal Mortality; Multicenter Study.



Christianne Bretas Vieira Scaramello, BPharm., M.Sc., Ph.D.
Associate Editor International Journal of Cardiovascular Sciences
Universidade Federal Fluminense - UFF

Mailing Address: Christianne Brêtas Vieira Scaramello
Instituto Biomédico - Universidade Federal Fluminense - Rua Prof. Hernani Mello, 101. Postal Code: 24210-130, São Domingos, Niterói, RJ - Brazil
E-mail: chrisbretas@gmail.com

DOI: https://doi.org/10.36660/ijcs.20210160

The project will be conducted in public and private hospitals with compatible infrastructure, a responsible researcher, and approval by the respective Ethics and Research Committees.[6]

An Investigation Committee, formed by members from the Department of Women's Cardiology of the Brazilian Society of Cardiology, will select the participating centers and coordinate the platform of the data record. The responsible researcher from each center will select patients according to the defined inclusion and exclusion criteria, manage incomplete data, insert data in the Research Electronic Data Capture (REDCap) platform, and participate in the Committee's meetings to contribute to study progress.[6]

In addition to the inclusion and exclusion criteria, the variables to be analyzed, outcomes, prospective sample size, and statistical analysis have been well defined in the proposal. Furthermore, data quality management and assurance have also been described. Thus, the proposal seems to be well outlined, presenting few specific limitations, which the authors have already mentioned. It is worth noting that the project has been approved by the Ethics and Research Committee of Hospital of the Clinics, Faculty of Medicine, University of São Paulo, which is the coordinating center of the study.[6]

A similar study was conducted by Roos-Hesselinket et al.[7] They observed that patients with cardiomyopathy and pulmonary arterial hypertension are high risk, while relatively good outcomes are expected for women with congenital heart disease. They stated that pregnancy should only be discouraged to women with very high risks. They also quoted some pre-pregnancy predictors for mortality and/or heart failure, such as NYHA class > II, systemic ventricular ejection fraction < 40%, signs of heart failure, and the use of anticoagulants. Roos-Hesselinket et al.[7] concluded that, after 2010, maternal mortality and/or heart failure rates decreased, particularly in emerging countries, despite the increased number of high-risk patients, highlighting the importance of further studies to assess the optimal management of these patients.

Brazil is a continent-sized country. The literature discusses that continental dimensions, heterogeneity, and wide local diversity have to be considered to define public policy and healthcare,[8-10] making the proposal by Avila et al.[6] even more remarkable, given that they intend to analyze the macroregions of the country.

References

1. Guimarães T, Magalhães A, Veiga A, Fiuza M, Ávila W, Pinto FJ. Heart Disease and Pregnancy: State of the Art. Rev Port Cardiol. 2019;38(5):373-83. doi: 10.1016/j.repc.2018.05.013.
2. Testa CB, Borges VTM, Bortolotto MRFL. Pregnancy in Patients With Heart Disease. Rev Med. 2018; 97(2):177-86. doi: 10.11606/issn.1679-9836.v97i2p177-186.
3. Avila WS, Alexandre ERG, Castro ML, Lucena AJG, Marques-Santo C, Freire CMV, et. al. Brazilian Cardiology Society Statement for Management of Pregnancy and Family Planning in Women with Heart Disease – 2020. Arq Bras Cardiol. 2020; 114(5):849-942. doi: 10.36660/abc.20200406.
4. Avila WS, Ribeiro VM, Rossi EG, Binotto MA, Bortolotto MR, Testa C, Francisco R, et al. Pregnancy in Women with Complex Congenital Heart Disease. A Constant Challenge Arq. Bras. Cardiol. 2019;113(6):1062-9. doi: 10.5935/abc.20190197.
5. Parsonage WA, Zentner D, Lust K, Kane SC, Sullivan EA. Heart Disease and Pregnancy: The Need for a Twenty-First Century Approach to Care…. Heart Lung Circ. 2021;30(1):45-51. doi: 10.1016/j.hlc.2020.06.021.
6. Avila W, Rivera MAM, Marques-Santos C, Rivera IR, Costa MENC, Lucena AJG, et al. The REBECGA Brazilian Registry of Pregnancy and Heart Disease: Rationale and Design. Int J Cardiovasc Sci. 2021; 34(4):452-458. doi: https://doi.org/10.36660/ijcs.20200419.
7. Roos-Hesselink J, Baris L, Johnson M, Backer J, Otto C, Marelli A, et al. Pregnancy Outcomes in Women with Cardiovascular Disease: Evolving Trends Over 10 years in the ESC Registry Of Pregnancy And Cardiac disease (ROPAC). Eur Heart J. 2019;40(47):3848-55. doi: 10.1093/eurheartj/ehz136.
8. Cecilio LCO, Reis AACD. Notes on Persistent Challenges for Basic Health Care in Brazil. Cad Saude Publica. 2018;34(8):e00056917. doi: 10.1590/0102-311X00056917.
9. Koga D. Experiencing territories in a continental country. Serv Soc Saude. 2015;14(1):9-26.
10. Busingye D, Arabshahi S, Subasinghe AK, Evans RG, Riddell MA, Thrift AG. Do the Socioeconomic and Hypertension Gradients in Rural Populations of Low- and Middle-Income Countries Differ by Geographical Region? A Systematic Review and Meta-Analysis. Int J Epidemiol. 2014;43(5):1563-77. doi: 10.1093/ije/dyu112.

ORIGINAL ARTICLE

Vegetarian Diets and Cardiovascular Risk in Women

Bianca Oliveira, Luciana Nicolau Aranha, Priscila dos Santos Gomes Olivares, Tamira Guilherme Rocha Negrão, Glorimar Rosa, Gláucia Maria Moraes de Oliveira

Universidade Federal do Rio de Janeiro, Rio de Janeiro – RJ – Brazil

Abstract

Background: Vegetarian diets have favorable effects on cardiovascular risk, provided that they do not contain ultra-processed foods (UPF).

Objective: To compare the metabolic profile, cardiovascular risk, body composition, and food consumption in vegan (VEG), lacto-ovo vegetarian (LOV), and omnivorous (OMNI) women. To verify the association between UPF consumption and cardiovascular risk.

Methods: Cross-sectional study with 119 VEG (n = 43), LOV (n = 38), and OMNI (n = 38) women. Anthropometric and biochemical parameters and the Framingham risk score were assessed. Food consumption was assessed by means of a 3-day food register, and intake of macronutrients, micronutrients, and UPF was estimated. The correlation between UPF consumption and cardiovascular risk was assessed using Spearman's coefficient, with a significance level of 5%.

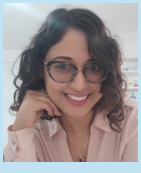
Results: The groups showed low cardiovascular risk, without significant difference between them. The VEG and LOV groups had lower body mass index, neck circumference, body shape index, and systolic blood pressure ($p < 0.05$) than the OMNI group; greater consumption of carbohydrates, sugars, dietary fibers, micronutrients, beta-carotene, and carotenoids; and lower consumption of total fat, saturated fatty acids, and cholesterol ($p < 0.05$). Consumption of UPF was lower in the LOV group (5.7 [0.0– 19.8]) than in the OMNI group (14.9 [5.1 – 22.3]; $p < 0.05$). UPF consumption was associated with SBP ($\varrho = 0.439$; $p = 0.007$) and blood sugar ($\varrho = 0.422$; $p = 0.010$) in the VEG group, and in the LOV group it was inversely associated with LDL-c ($\varrho = -0.456$; $p = 0.010$).

Conclusion: Vegetarian women showed better body composition and dietary quality than OMNI women. It is important to take consumption of UPF in vegetarians into consideration, in order to improve cardiovascular risk in women.

Keywords: Vegetarian Diet; Vegan; Women; Risk Factors; Industrialized Foods.

Introduction

Worldwide prevalence of cardiovascular disease (CVD) practically doubled from 271 million (95% uncertainty interval [UI]: 257 to 285 million) in 1990 to 523 million (95% UI: 497 to 550 million) in 2019, and the number of deaths due to CVD increased constantly from 12.1 million (95% UI: 11.4 to 12.6 million) in 1990 to 18.6 million (95% UI: 17.1 to 19.7 million) in 2019.[1] In young women, an increase has been observed in hospitalizations due to CVD and acute myocardial infarction, which has occurred mainly due to an increase in the prevalence of obesity and cardiometabolic risk factors.[2] In Brazil, according to



Bianca Oliveira, MSc
Master in Cardiovascular Sciences
Postgraduate program in Cardiology - UFRJ

Mailing Address: Gláucia Maria Moraes de Oliveira
Universidade Federal do Rio de Janeiro – R. Prof. Rodolpho P. Rocco, 255 – 8°. Andar – Sala 6, UFRJ.
Postal Code: 21941-913, Cidade Universitária, RJ – Brazil
E-mail: glauciamoraesoliveira@gmail.com

DOI: https://doi.org/10.36660/ijcs.20210010

Manuscript received January 17, 2021; revised manuscript May 11, 2021; accepted June 02, 2021.

data from the Informatics Department of the Unified Health System (DATASUS, acronym in Portuguese), in 2019, 17.2% of deaths that occurred in women of childbearing age were due to circulatory system diseases, thus representing the second leading cause of mortality in this group.[3]

Considering that the majority of cardiometabolic risk factors do not occur with clinical manifestations, early identification can be important in order to modify prognosis of CVD. Accordingly, some tools have been suggested to predict cardiovascular risk, such as the Framingham Risk Score (FRS), which assesses short-term risk of coronary artery disease (CAD), and traditional anthropometric indices, such as body mass index (BMI), waist circumference (WC), and waist-to-height ratio (WHR), as well as new indices, such as lipid accumulation product (LAP), body roundness index (BRI), and body shape index (ABSI).[4,5]

In relation to strategies for modifying the course of CVD, diet plays a crucial role. Different dietary patterns (DP) such as the Dietary Approaches to Stop Hypertension (DASH) eating plan, the Mediterranean DP, and the vegetarian DP have been proposed by the American Heart Association/American College of Cardiology (AHA/ACC) both for prevention and treatment of CVD and in general, emphasizing the increased consumption of vegetables, fruits, whole grains, and legumes and limited intake of red meat, sweets, sugar-sweetened beverages, and salty or highly processed foods.[6]

In recent years, the number of vegetarians has increased, and this DP has been associated with health benefits, given that it involves reduced cardiometabolic risk factors, and it may contribute to a lower prevalence of CVD.[7-9] The benefits of the vegetarian DP result from increased consumption of vegetables, sources of fiber, and phytonutrients, which reduce inflammation and oxidative stress, providing cardiovascular protection.[10]

Although plant-based diets have been associated with lower risk of CVD, they may not always have beneficial health effects, in the event that they are rich in unhealthy plant foods (sugar-sweetened juices/beverages, refined grains, fried potatoes, sweets).[11] It is known that consumption of ultra-processed foods (UPF) is associated with the main cardiovascular risk factors, such as obesity, hypertension, dyslipidemia, hyperglycemia, and hyperinsulinemia; reduced consumption of these foods is, therefore, recommended.[12] Few studies in the literature have investigated the consumption of UPF in vegetarians, especially in women.[13,14]

It is important to comprehend the nutritional profile of women and to compare different DPs in order to verify their associations with diseases, such as CVD, thus establishing nutritional behavior protocols for prevention. In this manner, the objective of this study was to compare the metabolic profile, cardiovascular risk, body composition, and food consumption in women who adhered to vegan (VEG), lacto-ovo–vegetarian (LOV), and omnivorous (OMNI) diets, as well as to verify consumption of UPF.

Individuals And Methods

Study Groups

This cross-sectional study was conducted between January and July 2019, with a convenience sample of 119 women selected at a clinical nutrition outpatient clinic, in Rio de Janeiro. Women ages 20 to 59 years old were selected; they had adhered to the DP for at least 6 months, and they were divided into the following groups: VEG (no consumption of any products of animal origin), LOV (consumption of eggs, milk, and dairy products), and OMNI (consumption of red meat, fish, chicken, eggs, milk, and dairy products. Pregnant and breastfeeding women were excluded.

This study received approval from the Ethics Committee of the Clementino Fraga Filho University Hospital of the Federal University of Rio de Janeiro, and it was registered under number 89033118.1.0000.5257. All participants signed a free and informed consent form.

Anthropometric, body composition, blood pressure, and cardiovascular risk assessment

Anthropometric assessment was carried out, including measurements of body mass in kg, height in m, waist circumference (WC) in cm, and neck circumference (NC) in cm. Body mass index (BMI) was calculated (weight/height^2) and classified in accordance with the parameters established by the World Health Organization.[15] The waist-to-height ratio (WHR),[16] visceral adiposity index (VAI),[17] LAP,[18] BRI,[19] and ABSI were also calculated and classified.[20]

Body composition was assessed by tetrapolar bioimpedance (Biodynamics 450,biodynamics corporation, Washington), and body fat percentage

was classified according to Lohman et al.[21]. Blood pressure was measured by the auscultatory method.[22] Cardiovascular risk was calculated by means of the FRS, using the standardized calculator (https://qxmd.com/calculate/calculator_253/framingham-risk-score-atp-iii), which takes the following variables into account: sex, age, total cholesterol, high-density lipoprotein (HDL), systolic blood pressure (SBP), use of medications for systemic arterial hypertension, and smoking.[4]

Biochemical Assessment

Blood samples were collected in the morning, after a 12-hour fasting period, in tubes with gel to obtain serum; 30 minutes after collection, blood samples were centrifuged for 15 minutes at 4,000 rpm. Serum concentrations of glucose, triglycerides, HDL, and total cholesterol were determined by the enzymatic method, using an automated biochemical analyzer (Labtest Diagnostica SA, Vista Alegre, Lagoa Santa – Mg. Brazil). Low-density lipoprotein (LDL) concentrations were calculated using the Friedewald formula.[23] Serum insulin concentration was obtained by chemiluminescence, and insulin resistance was estimated using the homeostasis model assessment of insulin resistance (HOMA-IR) index.[24]

Assessment of Food Consumption and Degree of Physical Activity

Consumption of energy, macronutrients, and micronutrients was assessed using a 3-day food register (2 typical and 1 atypical days), and data were analyzed using Food Processor software, version 7.2 (EshaResearch, Salem, MA, USA). Assessment of the adequacy of nutritional composition of micronutrients was based on Dietary Reference Intakes.[25] Adequate consumption of fiber, saturated fat, and sodium was established based on the guidelines of the Brazilian Society of Cardiology.[26] Consumption of processed foods and UPF was classified according to the NOVA classification, by Monteiro et al.[27]

Degree of physical activity was assessed by the short version of the International Physical Activity Questionnaire.[28]

Statistical Analysis

Statistical analyses were conducted using IBM® SPSS® Statistics software, version 25 (Armonk, NY, USA). Categorical variables were shown as percentages and analyzed using the chi-square (χ^2) test. Normality of variables was evaluated using the Kolmogorov-Smirnov method. Continuous variables were represented as median and interquartile range, because they did not show normal distribution. For comparison between groups, the Kruskal-Wallis test with post hoc Bonferroni was used. Spearman's correlation coefficients were used to evaluate correlations between percentage of total energy value from UPF and cardiovascular risk factors. Values were considered significant when $p < 0.05$.

Results

A total of 119 women were included in the study. Their characteristics are shown in Table 1. Of these participants, 43 (36%) were VEG, with median age of 29 (24 to 35) years; 38 (32%) were LOV, with median age of 27.5 (22 to 36) years; and 38 (32%) were OMNI, with median age of 33.5 (27 to 40) years. The VEG and LOV group had higher level of schooling than the OMNI group.

The prevalence of excess body mass (overweight or obesity) in the study population was 25.6% in VEG, 26.3% in LOV, and 57.8% in OMNI. Even though the cutoff values of the anthropometric indices were within adequate values for all groups, VEG and LOV had lower BMI, NC, and ABSI compared to OMNI. Furthermore, SBP was significantly lower in the groups that adhered to vegetarian DPs (VEG and LOV). Moreover, the LOV group had significantly lower WHR, WC, BRI, and DBP values than the OMNI group, and LDL-c concentrations were lower in the VEG group than in the OMNI group (Table 2).

With the aim of assessing short-term risk of CAD, the FRS was calculated, and it showed that all study groups had low (1%) risk of CAD in the short term (≤ 10 years), without any statistically significant difference ($p = 0.340$).

When assessing food consumption, it was observed that VEG and LOV had higher consumption of carbohydrates; sugars; dietary fiber; vitamins A, C, and E; potassium; beta-carotene; and carotenoids, as well as lower consumption of total fat, saturated fatty acids, cholesterol, sodium, and Na/Kcal ratio than the OMNI group. Moreover, UPF consumption was significantly lower in LOV (5.7 [0.0 – 19.8]) than in OMNI (14.9 [5.1 – 22.3]; $p < 0.05$), as can be observed in Table 3.

The correlation test between percentage of TEV from UPF and cardiovascular risk factors demonstrated that consumption of UPF was positively associated with SBP ($\rho = 0.439$; $p = 0.007$) and blood sugar ($\rho = 0.422$; $p = 0.010$) in the VEG group and negatively associated with

Table 1 – Sociodemographic characteristics according to type of diet adopted

	VEG (n 43)	LOV (n 38)	OMNI (n 38)	p value
Age (years)	29 (24-35)	27.5 (22-36)	33.5 (27-40)	0.07
Per capita income (MW)	0.03 (0.001-1.2)	0.7 (0.001 – 2)	1.5 (0.4-2)	0.20
Level of schooling (n, %)				
Primary Secondary Tertiary	(0) - 0% (2) - 4.7% (41) - 95.3%	(1) - 2.6% (3) - 7.9% (34) - 89.5%	(6) - 15.8% (11) - 28.9% (21) - 55.3%	**0.001**
Skin color (n - %)				
Black Mixed White	(4) - 9.3% (13) - 30.2% (26) - 60.5%	(2) - 5.3% (10) - 26.3% (26) - 68.4%	(7) - 18.4% (15) - 39.5% (16) - 42.1%	0.15
Duration of vegetarianism (years)	3 (1.2 – 5)	2 (1 – 4)	0 (0-0)	0.10
Nutritional follow-up (n, %)	(20) - 46.5%	(17) - 44.7%	(11) - 28.9%	0.22
Alcohol use	(22) - 51.2%	(20) - 52.6%	(10) - 26.3	0.06
Smoking	(0) - 0%	(2) - 5.3%	(2) - 5.3%	0.08
SAH	(0) - 0%	(1) - 2.6%	1- 2.6%	0.14
DM	(0) - 0%	(0) - 0%	(2) - 5.2%	0.11
CVD	(0) - 0%	(1) - 2.6%	(0) - 0%	0.17
Degree of physical activity (IPAQ)				
Active (n, %)	(33) - 76.6%	(24) - 63.2%	(23) - 62.5%	0.58
Sedentary (n, %)	(10) - 23.4%	(14) - 36.9%	(13) - 37.5%	

Values shown as median and interquartile range and frequency (n, %). Chi-square test for categorical variables. Kruskal-Wallis test with post hoc Bonferroni for continuous variables. Values considered statistically significant: $p < 0.05$. CVD: cardiovascular disease; DM: diabetes mellitus; IPAQ: International Physical Activity Questionnaire; LOV: lacto-ovo vegetarian; MW: minimum wage; OMNI: omnivorous; SAH: systemic arterial hypertension; VEG: vegan.

LDL-c ($\rho = -0.456$; $p = 0.010$) in the LOV group, as can be observed in Table 4. No associations were observed between UPF consumption and the FRS and 10-year risk of CVD in any of the groups.

The main results of this article can be seen in Figure 1.

Discussion

In this study, women who adhered to a vegetarian DP had better body composition and dietary quality, in comparison with the OMNI DP. In the VEG group, UPF consumption was associated with higher blood sugar and SBP.

Our sample was characterized by young women, who were apparently healthy, and the majority were active. Consequently, the FRS indicated low short-term risk of CAD for all groups, and the biochemical parameters were within the limits of normality. Navarro et al.[29] carried out a cross-sectional study, with 88 apparently healthy men (44 vegetarians and 44 omnivores), age ≥ 35 years, and they observed FRS < 10; however, they found that risk of CAD, assessed by the FRS, was lower in vegetarians, as were some cardiovascular risk factors, suggesting that a plant-based diet could be considered protective for cardiovascular health.

The identification of individuals who are susceptible to developing CVD is extremely important and, at the same time, challenging, especially in those who are asymptomatic. The performance of scores for predicting cardiovascular risk varies considerably between populations, and evidence that supports the use of cardiovascular risk scores for primary

Table 2 – Blood pressure, body composition, and biochemical data, according to type of diet adopted

Variables	VEG (n 43)	LOV (n 38)	OMNI (n 38)
BMI (kg/m²)	22.3 (20.2-25.2)	22.2 (20.9-25.2)	25 (22.4-28.9) [a.b]
Fat mass (%)	26.6 (24 -30.2)	26.4 (24.3-31.7)	27 (22.6-31.5)
Lean mass (%)	73.2 (69.4 – 75.8)	73.6 (67.9 – 75.7)	71.2 (66.0 – 76.5)
WHR	0.5 (0.4-0.5)	0.4 (0.4-0.5)	0.5 (0.4-0.5) [b]
WC (cm)	74 (69 -80.5)	73.5 (69 – 77.6)	80.5 (72.7-85.2) [b]
NC (cm)	31.5 (30.4-33)	32 (30.9-33.1)	33.6 (31-36) [a.b]
VAI	0.9 (0.7-1.3)	1.05 (0.8-1.4)	1.01 (0.7-1.6)
LAP	12.8 (7.04-19.2)	13.9 (8.2-22.2)	17.2 (10.9-29.8)
CI	1.1 (1.08-1.2)	1.1 (1.07-1.2)	1.1 (1.07-1.2)
ABSI	0.6 (0.5-0.6)	0.5 (0.5-0.6)	0.5 (0.4-0.5) [a.b]
BRI	1.4 (1.2-1.6)	1.4 (1.2-1.5)	1.6 (1.3-1.8) [b]
SBP (mmHg)	110 (100-110)	105 (100-110.5)	115 (110-120) [a.c]
DBP (mmHg)	70 (70-80)	70 (70-80)	80 (70-80) [b]
Blood glucose (mg/dL)	80 (73-89)	77 (70.8-86)	76 (68-83)
Insulin (mIU/mL)	8 (4.8-13)	8 (6.8-13.3)	11 (6.5-15)
HOMA-IR	1.7 (0.75-2.7)	1.6 (1.1-2.4)	2.1 (1.3-3)
Triglycerides (mg/dL)	75 (57-91)	79.5 (63-102.8)	74.5 (57.5-101)
TC (mg/dL)	162 (140-183)	175.5 (153.2-205.5)	181 (153-213.3)
LDL-c (mg/dL)	86 (70-104)	98 (80.3-118.3)	106 (86.7-123.5) [a]
HDL-c (mg/dL)	59 (49-68)	62 (47.8-70.3)	59 (47-67.3)

Values shown as median and interquartile range. Kruskal-Wallis test with post hoc Bonferroni to analyze significance level. Values considered statistically significant: $p < 0.05$. [a] $p < 0.05$ between OMNI and VEG; [b] $p < 0.05$ between OMNI and LOV; [c] $p \leq 0.001$ between OMNI and LOV. ABSI: body shape index; BMI: body mass index; BRI: body roundness index; CI: conicity index; DBP: diastolic blood pressure; HDL: high-density lipoprotein; LAP: lipid accumulation product; LDL: low-density lipoprotein; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides; VAI: visceral adiposity index; WC: waist circumference; WHR: waist-to-height ratio.

prevention is scarce.[30] Furthermore, women have sex-specific factors (early menarche, hormonal factors, autoimmune conditions, pregnancy-associated factors, etc.), which have demonstrated association with increased cardiovascular risk.[31] Accordingly, it is necessary to create new models in order to assess cardiovascular risk in this specific group and to determine the role of these scores in predicting cardiovascular risk in primary prevention.

When comparing DPs, studies have shown that vegetarians have lower BMI and WC than omnivores.[9,32] In a cohort of 49,098 adults in Taiwan, a lower prevalence of overweight was observed in vegetarians than in non-vegetarians; the authors also found that, for each year on a vegan diet, the risk of obesity decreased by 7%.[33] We also found that omnivores had more overweight and greater WC, NC, WHR, ABSI, and BRI than vegetarians. New anthropometric indices have been used to assess the risk of CVD; the BRI, for example, is an index based on WC and height, and it has demonstrated a good capacity for identifying risk of CAD in women;[5] there are, however, no studies in the literature that compare these new indices in vegetarians and non-vegetarians.

Different DPs, and food choices may contribute to the development of diseases, and food choices may contribute to the development of diseases. In this study, we observed that the VEG and LOV groups had more balanced diets that were rich in fibers and adequate in terms of nutrients,

Table 3 – Food consumption according to type of diet adopted

Variable	VEG	LOV	OMNI
Energy (kcal)	1751.9 (1348.7-2231.2)	1431.2 (1119.5-1861.6)	1447.7(1155.7-1711.2) [a]
Processed foods (% TEV)	8.8 (0.4-14.4)	5.7 (0.0-19.8)	14.9 (5.1-22.3)
Ultra-processed foods (% TEV)	2.7 (0.0-9.3)	0.0 (0.0-4.2)	6.3 (0.0-24.4) [b]
Proteins (% TEV)	12.7 (11.1 – 16.4)	15.6 (12.3 – 20.6) [f]	19.5 (22.5 – 29.7) [d]
Carbohydrates (% TEV)	65.7 (59.5 – 72.9)	62.3 (57.1 – 70.2)	49.5 (43.2 – 54.5) [d, e]
Sugars (% TEV)	15.1 (10.9 – 20.7)	12.0 (9.7 – 19.4)	7.1 (5.0 – 10.8) [b,d]
Dietary fiber (g)	42.5 (34.7-52)	35.1 (26.9-45.7)	13.8 (11.9- 22.3) [d,e]
Total fats (% TEV)	22.7 (16.2 – 25.8)	20.7 (14.0 – 29.5)	28.4 (23.5 – 30.3) [a,b]
Saturated fatty acids (% TEV)	3.4 (2.7-4.4)	5.1 (3.0-7.1)	10.5 (8.9-12.5) [d,e]
Monounsaturated fatty acids (% TEV)	5.0 (3.0 – 7.5)	3.1 (1.7 – 5.5)	6.2 (4.1 – 7.6) [b]
Polyunsaturated fatty acids (% TEV)	2.3 (1.0 -3.3)	2.4 (1.6 – 3.3)	1.7 (1.1 – 2.3)
Cholesterol (mg)	10.5 (0.0 – 23.2)	25.0 (10.1 – 64.9) [c]	216.9 (158.9-272.7) [d,e]
Omega-6/omega-3 ratio	3.9 (1.6-8.1)	4.3 (2.1-8.2)	5.5 (4.2-8.4)
Sodium (mg)	1152 (854.2-1705.1)	1010.7 (771.1-1479.3)	1548.7 (1154.7-2148.4) [a,b]
Na/Kcal ratio	0.7 (0.5-0.98)	0.7 (0.6-1.07)	1.3 (0.96-1.68) [d,e]
Folic acid (mcg)	341.1 (225.4-507)	280.9 (143.3-408.5)	236.3 (144.7-356.3) [a]
Vitamin A (IU)	9958.8 (6016.9 - 12130.4)	10230.8 (4365.1 - 13978.8)	3141.5 (1579.6-9180.6)
Vitamin B_{12} (mcg)	0.04 (0.00 -0.77)	0.2 (0.08-0.30)	2.2 (1.06-3.8) [d,e]
Vitamin C (mg)	82.8 (48.8-127.9)	75.7 (41.1-159.2)	20.4 (12.0-66.1) [d,e]
Vitamin D (IU)	0. 0 (0.0 – 0.2)	1.6 (0.1-4.8) [c]	9.6 (5.9-25.7) [d,e]
Vitamin E (mg)	2.8 (1.5-5.6)	1.3 (0.97-2.2)	1.1 (0.7-1.8) [c,d]
Calcium (mg)	339.1 (257.4-512.6)	380.3 (278.7-497.1)	307.9 (185.7-369.7)
Iron (mg)	15.4 (11.8-18.8)	12.7 (9.8-18.3)	11.3 (8.9-14.7) [a]
Magnesium (mg)	235.6 (196.7-339.6)	213.4 (131.3-258.6)	135.6 (113.7 – 249.6) [a]
Potassium (mg)	1969.6 (1410.6-2615.5)	1759.9 (1309.1-2288)	1308.3 (947.1-1611.6) [a,b]
Zinc (mg)	4.3 (3.6-5.5)	3.9 (2.5-5.1)	5.9 (5.2-10.6) [a]
Beta-carotene (mg)	4.2 (1.6-6.3)	3.4 (2 - 6.2)	1.4 (0.3-2.3) [d,e]
Carotenoids (mg)	987.4 (519.7 – 1212.5)	1015.6 (366.3-1318.4)	261 (94.5 – 523.2) [d,e]

Values shown as median and interquartile range. Kruskal-Wallis test with post hoc Bonferroni to analyze significance level. Values considered statistically significant: $p < 0.05$. [a] $p < 0.05$ between OMNI and VEG; [b] $p < 0.05$ between OMNI and LOV; [c] $p < 0.05$ between LOV and VEG; [d] $p \leq 0.0001$ between OMNI and VEG; [e] $p \leq 0.0001$ between OMNI and LOV; [f] $p \leq 0.001$ between LOV and VEG. TEV: total energy value.

such as vitamins A, C, and E and carotenoids, and low in saturated fatty acids, cholesterol, and sodium. Bowman et al.[34] also observed differences between the vegetarian and omnivorous DPs; the first was characterized by greater consumption of micronutrients and lower consumption of saturated fat and sodium.

Greater intake of fruits, vegetables, and legumes is associated with lower risk of CVD, acute myocardial infarction, cardiovascular mortality, non-cardiovascular mortality, and total mortality. This is because these foods contain antioxidants and polyphenols, such as vitamin C, vitamin E, and carotenoids, which can prevent lipid

Table 4 – Spearman correlation between percentage of total energy value from ultra-processed foods and cardiovascular risk factors, by dietary group

	VEG		LOV		OMNI	
	ϱ	p value	ϱ	p value	ϱ	p value
BMI (kg/m²)	−0.123	0.473	0.240	0.193	−0.082	0.661
Fat mass (%)	−0.161	0.348	0.047	0.802	−0.044	0.813
WHR	−0.18	0.917	0.083	0.657	0.137	0.463
WC (cm)	−0.019	0.193	0.113	0.546	0.116	0.534
NC (cm)	0.033	0.847	0.121	0.516	−0.216	0.243
VAI	−0.043	0.804	0.050	0.788	0.183	0.325
LAP	−0.023	0.894	0.116	0.534	0.131	0.482
CI	0.049	0.777	−0.075	0.690	0.297	0.105
ABSI	0.174	0.310	−0.303	0.098	0.237	0.200
BRI	−0.052	0.764	0.099	0.596	0.123	0.510
SBP (mmHg)	**0.439***	**0.007**	0.011	0.951	−0.157	0.399
DBP (mmHg)	0.178	0.299	−0.096	0.607	−0.299	0.103
Blood sugar (mg/dL)	**0.422***	**0.010**	−0.015	0.934	0.040	0.829
Insulin (mIU/mL)	0.003	0.988	0.066	0.748	0.002	0.993
HOMA-IR	0.094	0614	0.086	0.675	0.017	0.935
Triglycerides (mg/dL)	0.069	0.691	0.033	0.859	0.105	0.572
TC (mg/dL)	0.025	0.886	−0.293	0.110	−0.127	0.497
LDL-c (mg/dL)	−0.121	0.480	**−0.456***	**0.010**	−0.097	0.605
HDL-c (mg/dL)	0.236	0.165	−0.87	0.641	−0.054	0.774

Values considered statistically significant: p < 0.05. ABSI: body shape index; BMI: body mass index; BRI: body roundness index; CI: conicity index; DBP: diastolic blood pressure; HDL: high-density lipoprotein; HOMA-IR: homeostasis model assessment of insulin resistance; LAP: lipid accumulation product; LDL: low-density lipoprotein; SBP: systolic blood pressure; TC: total cholesterol; TG: triglycerides; VAI: visceral adiposity index; WC: waist circumference; WHR: waist-to-height ratio.

oxidation in the arterial vessel walls, reduce blood pressure, and improve endothelial function, in addition to the fibers that are associated with reduced insulin, total cholesterol, and LDL.[35] In contrast, saturated fatty acids influence the production of inflammatory cytokines and insulin resistance, and sodium increases blood pressure; consequently, increased consumption of these nutrients is associated with increased cardiovascular mortality.[36-38]

Although vegetarian diets are favorable to health,[8,39] they may often not bring health benefits in the event that they are composed of processed foods.[11] We observed greater consumption of UPF in the OMNI group, in comparison with LOV. The VEG group, even though they had low consumption of UPF, had elevated sugar intake (> 10% of TEV). Silveira et al.[13] studied 503 vegetarians (83.7% women), and they observed that 60% consumed UPF and sugar-sweetened beverages; the frequency of excess daily intake of UPF (≥ 3 times daily) and sugar-sweetened beverages (≥ 3 times daily) were 16% and 20%, respectively. Furthermore, excessive consumption of UPF (≥ 3 times daily) was independently associated with overweight. A recent cross-sectional study of the NutriNet-Santé cohort, conducted in France with 21,212 participants with different DP (omnivorous, pesco-vegetarian, vegetarian, and vegan), found that increased avoidance of foods of animal origin was associated with increased consumption of UPF, demonstrating that not

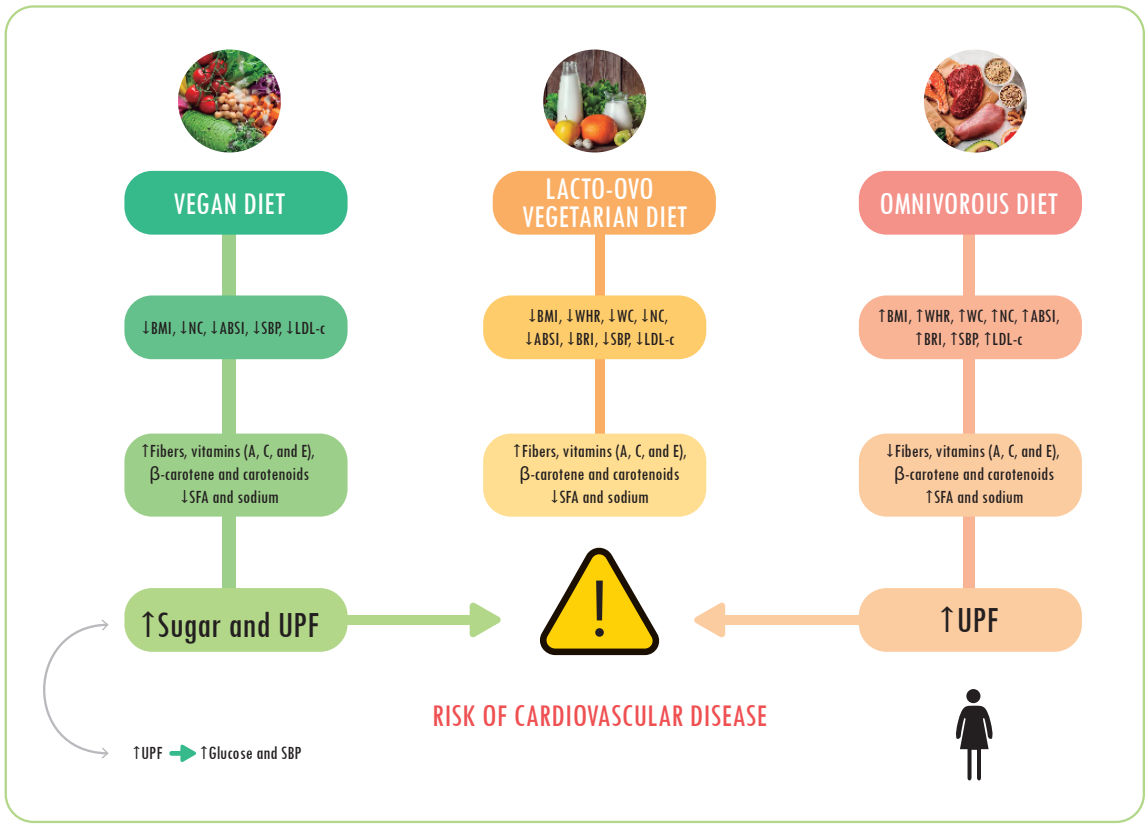


Figure 1 – Effect of dietary pattern on cardiovascular risk in women.
ABSI: body shape index; BMI: body mass index; BRI: body roundness index;LDL: low-density lipoprotein; NC: neck circumference; SBP: systolic blood pressure; SFA: saturated fatty acids; UPF: ultra-processed foods; WC: waist circumference; WHR: waist-to-height ratio.

all vegetarian diets necessarily bring health benefits, due to the potential effects of UPF.

We observed an association of UPF consumption with SBP and blood sugar in the VEG group. UPF are energy-dense, and they usually have higher total fat, saturated fat, sugar, and salt contents, as well as a lower amount of fiber and vitamins. High consumption of UPF is associated with increased prevalence of obesity, dyslipidemia, metabolic syndrome, and CVD.[12,40] It is, accordingly, necessary to reduce consumption of these foods, regardless of the DP adopted.

Study limitations include the small number of volunteers, which can make it difficult to generalize the results. Participants were young, apparently healthy, and active; it is likely due to this that they did not show alterations in biochemical parameters and had low FRS scores. The lack of a tool to assess cardiovascular risk in young women is also a limitation in the current literature. Finally, the cross-sectional study design limits the capacity to establish a causal association, making it necessary to conduct prospective longitudinal studies in the future in order to confirm these results. Nonetheless, this was the first Brazilian study to characterize UPF consumption and associate it with cardiovascular risk factors in vegetarian women, comparing them with other DPs.

Conclusion

Women who adhered to vegetarian DP had better body composition and dietary quality than those with OMNI DP, suggesting that the former DP can confer benefits with respect to cardiovascular protection in young women. Nevertheless, future studies should consider consumption of UPF in vegetarians as a modifiable risk factor for CVD.

Author contributions

Conception and design of the research: Oliveira BS, Aranha LN, Olivares PSG, Negrão TGR, Rosa G, Oliveira GMM. Acquisition of data: Oliveira BS, Aranha LN, Olivares PSG, Negrão TGR, Rosa G, Oliveira GMM. Analysis and interpretation of the data: Oliveira BS, Aranha LN, Olivares PSG, Negrão TGR, Rosa G, Oliveira GMM. Statistical analysis: Aranha LN, Rosa G, Oliveira GMM. Writing of the manuscript: Oliveira BS, Aranha LN, Olivares PSG, Negrão TGR, Rosa G, Oliveira GMM. Critical revision of the manuscript for intellectual content: Aranha LN, Rosa G, Oliveira GMM.

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 Bianca da Silva Oliveira, from *Universidade Federal do Rio de Janeiro.*

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Hospital Universitário Clementino Fraga Filho* under the protocol number 89033118.1.0000.5257. 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. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982-3021. doi: 10.1016/j.jacc.2020.11.010.
2. Arora S, Stouffer GA, Kucharska-Newton AM, Qamar A, Vaduganathan M, Pandey A, et al. Twenty Year Trends and sex Differences in Young Adults Hospitalized With Acute Myocardial Infarction. Circulation. 2019;139(8):1047-56. doi: 10.1161/CIRCULATIONAHA.118.037137.
3. Tabnet.datasus.gov [Internet]. Brasília: Ministério da Saúde; 2021 [cited 2021 Jan 05]. Available from: http://tabnet.datasus.gov.br/cgi/deftohtm.exe?sim/cnv/mat10uf.def.
4. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of Coronary Heart Disease Using Risk Factor Categories. Circulation. 1998;97(18):1837-47. doi: 10.1161/01.cir.97.18.1837.
5. Wang F, Chen Y, Chang Y, Sun G, Sun Y. New Anthropometric Indices or Old Ones: Which Perform Better in Estimating Cardiovascular Risks in Chinese Adults. BMC Cardiovasc Disord. 2018;18(1):14. doi: 10.1186/s12872-018-0754-z.
6. Van Horn L, Carson JA, Appel LJ, Burke LE, Economos C, Karmally W, et al. Recommended Dietary Pattern to Achieve Adherence to the American Heart Association/American College of Cardiology (AHA/ACC) Guidelines: A Scientific Statement from the American Heart Association. Circulation. 2016;134(22):505-29. doi: 10.1161/CIR.0000000000000462.
7. Rizzo NS, Jaceldo-Siegl K, Sabate J, Fraser GE. Nutrient Profiles of Vegetarian and Nonvegetarian Dietary Patterns. J Acad Nutr Diet. 2013;113(12):1610-9. doi: 10.1016/j.jand.2013.06.349.
8. Dinu M, Abbate R, Gensini GF, Casini A, Sofi F. Vegetarian, Vegan Diets and Multiple Health Outcomes: A Systematic Review With Meta-Analysis of Observational Studies. Crit Rev Food Sci Nutr. 2017;57(17):3640-9. doi: 10.1080/10408398.2016.1138447.
9. Benatar JR, Stewart RAH. Cardiometabolic Risk Factors in Vegans; A Meta-Analysis of Observational Studies. PLoS One. 2018;13(12):e0209086. doi: 10.1371/journal.pone.0209086.
10. Kahleova H, Levin S, Barnard ND. Vegetarian Dietary Patterns and Cardiovascular Disease. Prog Cardiovasc Dis. 2018;61(1):54-61. doi: 10.1016/j.pcad.2018.05.002.
11. Satija A, Bhupathiraju SN, Spiegelman D, Chiuve SE, Manson JE, Willett W, et al. Healthful and Unhealthful Plant-Based Diets and the Risk of Coronary Heart Disease in U.S. Adults. J Am Coll Cardiol. 2017;70(4):411-22. doi: 10.1016/j.jacc.2017.05.047.
12. Monteiro CA, Cannon G, Levy RB, Moubarac JC, Louzada ML, Rauber F, et al. Ultra-Processed Foods: What They are and How to Identify Them. Public Health Nutr. 2019;22(5):936-41. doi: 10.1017/S1368980018003762.
13. Silveira JAC, Meneses SS, Quintana PT, SANTOS VS. Association Between Overweight and Consumption of Ultra-Processed Food and Sugar-Sweetened Beverages Among Vegetarians. Rev. Nutri., Campinas, 30(4):431-41. doi: https://doi.org/10.1590/1678-98652017000400003.
14. Gehring J, Touvier M, Baudry J, Julia C, Buscail C, Srour B, et al. Consumption of Ultra-Processed Foods by Pesco-vegeTarians, Vegetarians, and Vegans: Associations with Duration and Age at Diet Initiation. J Nutr. 2021;151(1):120-31. doi: 10.1093/jn/nxaa196.
15. World Health Organization. Obesity: Preventing and Managing the Global Epidemic - Report of a WHO Consultation. Geneva: World Health Organization; 2000.
16. Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica. Diretrizes Brasileiras de Obesidade: Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica. São Paulo: ABESO; 2016.
17. Amato MC, Giordano C. Visceral Adiposity Index: an Indicator of Adipose Tissue Dysfunction. Int J Endocrinol. 2014;2014:730827. doi: 10.1155/2014/730827.
18. Nascimento JXPT, Chein MBC, Sousa RML, Ferreira AS, Navarro PA, Brito LMO. Importance of lipid Accumulation Product Index as a Marker of CVD Risk in PCOS Women. Lipids Health Dis. 2015;14:62. doi: 10.1186/s12944-015-0061-y.
19. Liu XZ, Qian JD, Li HH, Wang LJ, Wu MK, Wang Q, et al. Body Roundness Index is Significantly Associated with Prehypertension and Hypertension in Nonobese Chinese Subjects. Biomed Environ Sci. 2019;32(11):854-9. doi: 10.3967/bes2019.106.
20. Dhana K, Kavousi M, Ikram MA, Tiemeier HW, Hofman A, Franco OH. Body Shape Index in Comparison with other Anthropometric Measures in Prediction of Total And Cause-Specific Mortality. J Epidemiol Community Health. 2016;70(1):90-6. doi: 10.1136/jech-2014-205257.

21. Lohman TG, Roche AF, Martorell R. Anthropometric Standardization Reference Manual. Champaign: Human Kinetics; 1988.

22. Malachias MVB, Gomes MAM, Nobre F, Alessi A, Feitosa AD, Coelho EB. 7th Brazilian Guideline of Arterial Hypertension: Chapter 2 - Diagnosis and Classification. Arq Bras Cardiol. 2016;107(3 Suppl 3):7-13. doi: 10.5935/abc.20160152.

23. 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.

24. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis Model Assessment: Insulin Resistance and Beta-Cell Function from Fasting Plasma Glucose and Insulin Concentrations in Man. Diabetologia. 1985;28(7):412-9. doi: 10.1007/BF00280883.

25. Otten J, Helliwig JP, Meyers LD. The Dietary Reference Intakes: The Essential Guide to Nutrient Requirements. Washington: National Academies Press; 2006.

26. Précoma DB, Oliveira GMM, Simão AF, Dutra OP, Coelho OR, Izar MCO, et al. Atualização da Diretriz de Prevenção Cardiovascular da Sociedade Brasileira de Cardiologia – 2019. Arq Bras Cardiol. 2019; 113(4):787-891. doi: 10.5935/abc.20190204

27. Monteiro CA, Cannon G, Moubarac JC, Levy RB, Louzada MLC, Jaime PC. The UN Decade of Nutrition, the NOVA Food Classification and the Trouble with Ultra-Processing. Public Health Nutr. 2018;21(1):5-17. doi: 10.1017/S1368980017000234.

28. Matsudo M, Araújo T, Matsudo V, Andrade D, Andrade E, Oliveira LC, et al. Questionário Internacional de Atividade Física (IPAQ): Estudo de Validade e Reprodutibilidade no Brasil. Ativ. Física e Saúde. 2001;6(1):5-18. doi: https://doi.org/10.12820/rbafs.v.6n2p5-18.

29. Navarro JCA, Antoniazzi L, Oki AM, Bonfim MC, Hong V, Bortolotto LA, et al. Prevalence of Metabolic Syndrome and Framingham Risk Score in Apparently Healthy Vegetarian and Omnivorous Men. Arq Bras Cardiol. 2018;110(5):430-7. doi: 10.5935/abc.20180073.

30. Brindle P, Beswick A, Fahey T, Ebrahim S. Accuracy and Impact of Risk Assessment in the Primary Prevention of Cardiovascular Disease: A Systematic Review. Heart. 2006;92(12):1752-9. doi: 10.1136/hrt.2006.087932.

31. Freaney PM, Khan SS, Lloyd-Jones DM, Stone NJ. The Role of Sex-Specific Risk Factors in the Risk Assessment of Atherosclerotic Cardiovascular Disease for Primary Prevention in Women. Curr Atheroscler Rep. 2020;22(9):46. doi: 10.1007/s11883-020-00864-6.

32. Jin Y, Kanaya AM, Kandula NR, Rodriguez LA, Talegawkar SA. Vegetarian Diets are Associated with Selected Cardiometabolic Risk Factors Among Middle-OLDER Aged South Asians in the United States. J Nutr. 2018;148(12):1954-60. doi: 10.1093/jn/nxy217.

33. Chiu YF, Hsu CC, Chiu TH, Lee CY, Liu TT, Tsao CK, et al. Cross-secTional and Longitudinal Comparisons of Metabolic Profiles between Vegetarian and non-Vegetarian Subjects: A Matched Cohort Study. Br J Nutr. 2015;114(8):1313-20. doi: 10.1017/S0007114515002937.

34. Bowman SA. A Vegetarian-Style Dietary Pattern is Associated with Lower Energy, Saturated Fat, and Sodium Intakes; and Higher Whole Grains, Legumes, Nuts, and Soy Intakes by Adults: National Health and Nutrition Examination Surveys 2013-2016. Nutrients. 2020;12(9):2668. doi: 10.3390/nu12092668.

35. Miller V, Mente A, Dehghan M, Rangarajan S, Zhang X, Swaminathan S, et al. Fruit, Vegetable, and Legume Intake, and Cardiovascular Disease and Deaths in 18 Countries (PURE): A Prospective Cohort Study. Lancet. 2017;390(10107):2037-49. doi: 10.1016/S0140-6736(17)32253-5.

36. Wang Q, Afshin A, Yakoob MY, Singh GM, Rehm CD, Khatibzadeh S, et al. Impact of Nonoptimal Intakes of Saturated, Polyunsaturated, and Trans Fat on Global Burdens of Coronary Heart Disease. J Am Heart Assoc. 2016;5(1):e002891. doi: 10.1161/JAHA.115.002891.

37. Kennedy A, Martinez K, Chuang CC, LaPoint K, McIntosh M. Saturated Fatty Acid-Mediated Inflammation and Insulin Resistance in Adipose Tissue: Mechanisms of Action and Implications. J Nutr. 2009;139(1):1-4. doi: 10.3945/jn.108.098269.

38. Otto MCO, Afshin A, Micha R, Khatibzadeh S, Fahimi S, Singh G, et al. The Impact of Dietary and Metabolic Risk Factors on Cardiovascular Diseases and Type 2 Diabetes Mortality in Brazil. PLoS One. 2016;11(3):e0151503. doi: 10.1371/journal.pone.0151503.

39. Huang T, Yang B, Zheng J, Li G, Wahlqvist ML, Li D. Cardiovascular Disease Mortality and Cancer Incidence in Vegetarians: A Meta-Analysis and Systematic Review. Ann Nutr Metab. 2012;60(4):233-40. doi: 10.1159/000337301.

40. Srour B, Fezeu LK, Kesse-Guyot E, Allès B, Méjean C, Andrianasolo RM, et al. Ultra-Processed Food Intake and Risk of Cardiovascular Disease: Prospective Cohort Study (NutriNet-Santé). BMJ. 2019;365:l1451. doi: 10.1136/bmj.l1451.

REVIEW ARTICLE

Closing the Gender Gap in Ischemic Heart Diseases and Myocardial Infarction

Maria Cristina Meira Ferreira,[1] Mayara Viana de Oliveira,[2] Maria Sanali Moura Paiva,[3] Viviana Lemke,[4] Fernanda Mangione,[5] Gláucia Maria Moraes de Oliveira[6]

Instituto Nacional de Cardiologia,[1] Rio de Janeiro, RJ – Brazil
Universidade Federal do Maranhão,[2] Imperatriz, MA – Brazil
Universidade Federal do Rio Grande do Norte,[3] Natal, RN – Brazil
Cardiocare, [4] Curitiba, PR – Brazil
Hospital Beneficência Portuguesa de São Paulo,[5] São Paulo, SP – Brazil
Universidade Federal do Rio de Janeiro,[6] Rio de Janeiro, RJ – Brazil

Cardiovascular diseases (CVD) remain the leading cause of morbidity and mortality in women worldwide. Especially for women, traditional risk factors fail to explain most cases, deaths, and disability-adjusted life years (DALYs) from CVD. Risk factors inherent to the female sex and psychosocial aspects play an essential role in the development of CVD in women. Efforts need to be made to narrow the gap in diagnosis and treatment among women, especially younger ones, among whom CVD prevalence is increasing worldwide.[1]

Ischemic heart disease (IHD) remains a major threat to public health, and the overall burden is increasing globally. The GBD 2019 Study estimated 126.5 (95% UI, 118.6-134.7) million prevalent cases of IHD in 2019 globally. Age-standardized rates for DALYs, deaths, and prevalent cases declined from 1990 to 2019, probably due to population growth and aging.[2] In addition, IHD was the leading cause of death and DALYs in Brazil in 2019 for both males (12.22% of total death – 95% UI, 11.5%-12.77%; annual percent change -0.022) and females (12.03% of total death – 95% UI, 10.66%-12.88%; annual percent change 0.07). It is important to note that there has been an increase in the annual percent change in mortality from IHD in women in recent years (Figure 1).[3]

The GBD 2017 estimated 1736 (95% UI, 1689-1779) DALYs lost per 100 000 individuals due to IHD, with lower rates for females (1127; 95% UI, 1084-1163) than for males (2153; 95% UI, 2067-2216), in 2017 in Brazil. From 1990 to 2017, there was a decline in DALYs lost for both males (-47%) and females (-52%) in all Brazilian Federative Units (Figure 2).[4]

In addition, the GBD 2017 estimated 84 events of IHD per 100 000 inhabitants in 2017 in Brazil. The age-standardized incidence was 104 per 100 000 inhabitants for males and 58 per 100 000 for females.[4] The GBD 2017 estimated a prevalence of IHD in 2017 of 2229 (95% UI, 2098-2372) and 1008 (95% UI, 938-1081) per 100 000 inhabitants for males and females, respectively. The IHD prevalence increased in both sexes from 1990 to 2017 (Figure 3).[4]

Mortality due to myocardial infarction

Myocardial infarction (MI) is the leading cause of death in Brazil nowadays. The MI mortality rate decreased between 1996 and 2019, in both sexes, especially among females, being more relevant in the state capitals than in the inner areas.[4]

According to the Brazilian Unified Health System (SUS) Department of Information Technology (DATASUS), there were 142 982 hospital admissions for MI in 2018, with in-hospital mortality of 11%. In 2018, the DATASUS registered 10 811 primary angioplasties for MI, with in-hospital mortality of 6.3% and a mean length of hospital stay of 5.1 days. In 2018, the total amount reimbursed for coronary

Keywords

Cardiovascular Disease; Myocardial Ischemia; Myocardial Infarction; Mortality; Prevalence; Disability-Adjusted Life Years (DALY).

Maria Cristina Meira Ferreira
Cardiologist Physician - Interventional Cardiologist
Instituto Nacional de Cardiologia

Mailing Address: Gláucia Maria Moraes de Oliveira
Universidade Federal do Rio de Janeiro – R. Prof. Rodolpho P. Rocco, 255 – 8°. Andar – Sala 6, UFRJ. Postal Code: 21941-913, Cidade Universitária, RJ – Brazil
E-mail: glauciam@cardiol.br, glauciamoraesoliveira@gmail.com

DOI: https://doi.org/10.36660/ijcs.20210001

Manuscript received on January 03, 2021; reviewed on March 06, 2021; accepted on April 07, 2021.

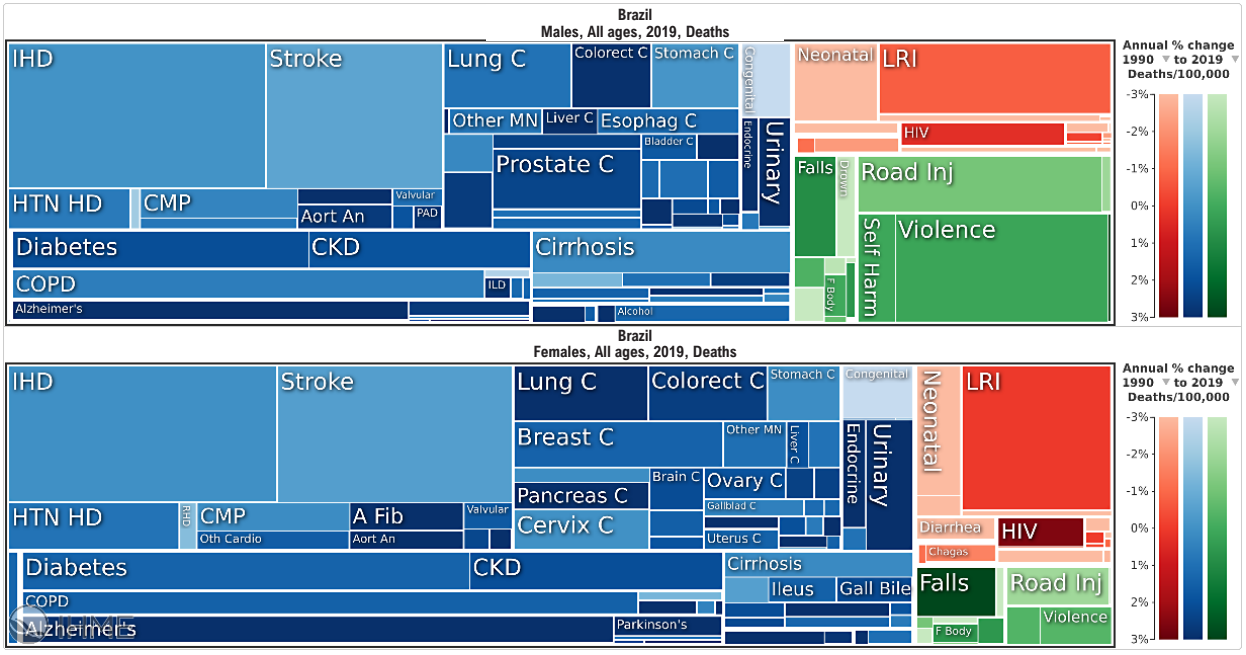


Figure 1 – Death according to causes in 2019 and annual percent change from 1990 to 2019, for both sexes, all ages.[3]

interventional procedures by the SUS was R$ 569 314 580 (Int$ 280 727 110), of which R$ 73 429 322 (13%) (Int$ 36 202 821) were for primary angioplasties.[4]

In 2019 there were 56 559 deaths from MI in men and 38 991 in women, totaling 95 550 deaths from MI. Most deaths occurred in the Southeast region, followed by the Northeast and South regions, with higher rates for males. The ratio between the gross rates of men and women in Brazil in 2019 was 1.49 (varying from 1.4 in the Southeast region to 1.8 in the Northeast region). These differences were less pronounced in older ages because of the female population aging.[5]

Pathophysiology and clinical implications

Myocardial infarction occurs mostly because of atherosclerotic plaque rupture with endothelial denudation, followed by sub-endothelial material exposure to bloodstream, triggering the coagulation process, with local formation of coronary thrombus and occlusion. This phenomenon of plaque rupture occurs in 76% of men and 55% of women. Considering the age of MI presentation, we can say that plaque rupture is rare in the premenopausal period.[6,7] Several other pathophysiologies account for half of the other cases in women.[6]

The second most common cause of MI is plaque erosion, which is more prevalent in women and occurs both in post- and premenopause. Unlike rupture, it does not lead to endothelial denudation. Optical coherence tomography (OCT) has identified that plaque rupture occurs in thin capsule plaques with more abundant necrotic nuclei, typically called thin capsule fibroatheroma. In contrast, plaque erosion occurs in plaques with a larger fibrotic component and smaller necrotic core. Thrombus visualization by OCT in these two different pathophysiological situations has shown that the thrombi in plaque erosions are characteristically older and present for more days at the erosion site, leading to a more significant occurrence of thromboembolic phenomena.[6,7]

Whether differences between plaque rupture and plaque erosion require different therapies is still an open field of study. We know that primary angioplasty with stenting substantially modifies the clinical outcome of patients with MI. However, whether stents are equally effective in both pathophysiologies mentioned above is yet to be answered.

The diagnosis of MI in the absence of obstructive coronary disease or with vessel stenosis smaller than 50%, known as MINOCA (myocardial infarction with nonobstructive coronary arteries), occurs five times more frequently in women, based on the VIRGO Study.[8] In 1/3 of the cases, MI presents as ST-elevation MI (STEMI) and

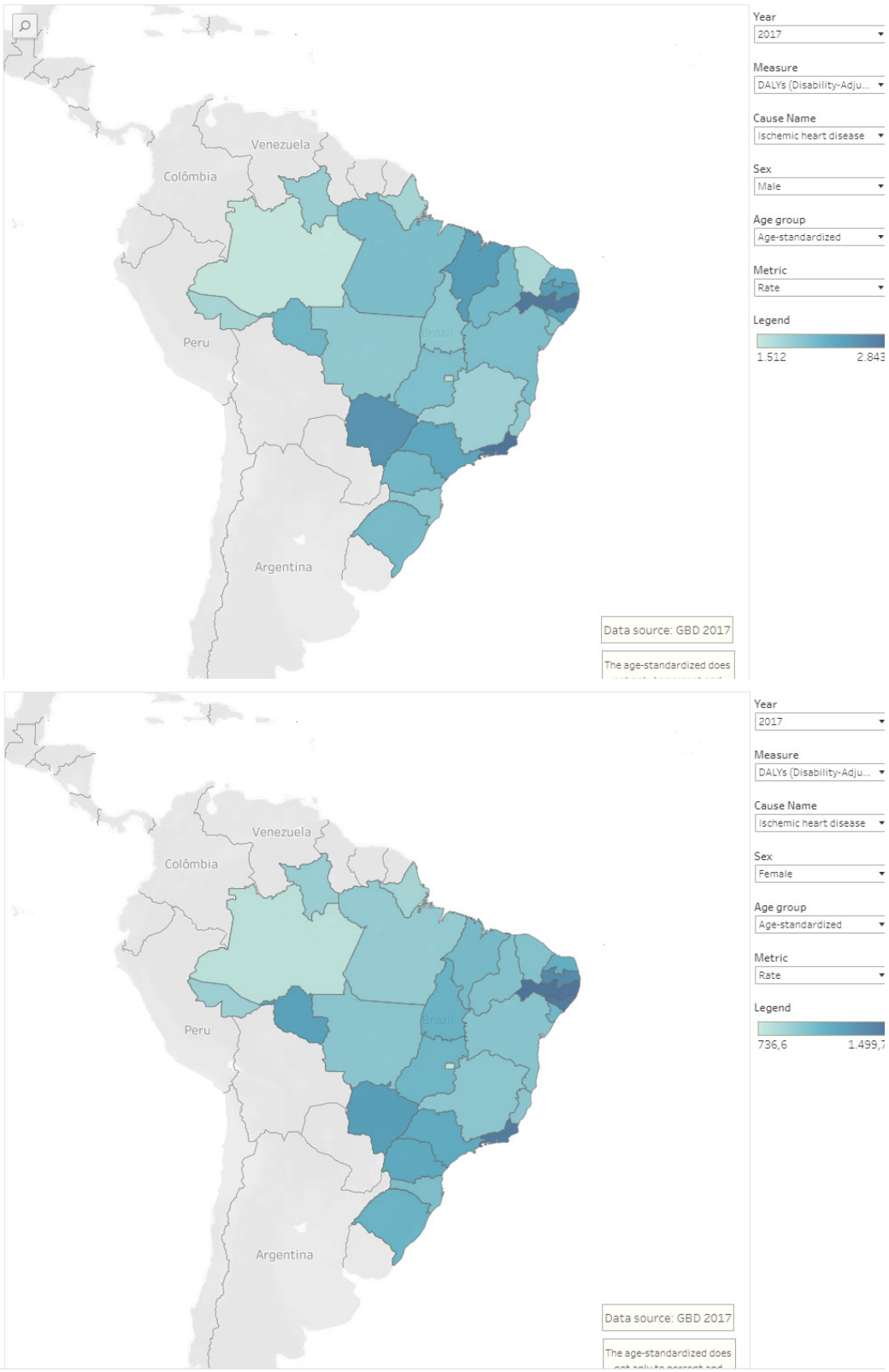


Figure 2 – Age-standardized DALYs, male (A) and female (B), per 100 000 inhabitants, due to IHD in 2017 and annual percent change from 1990 to 2017.[4]

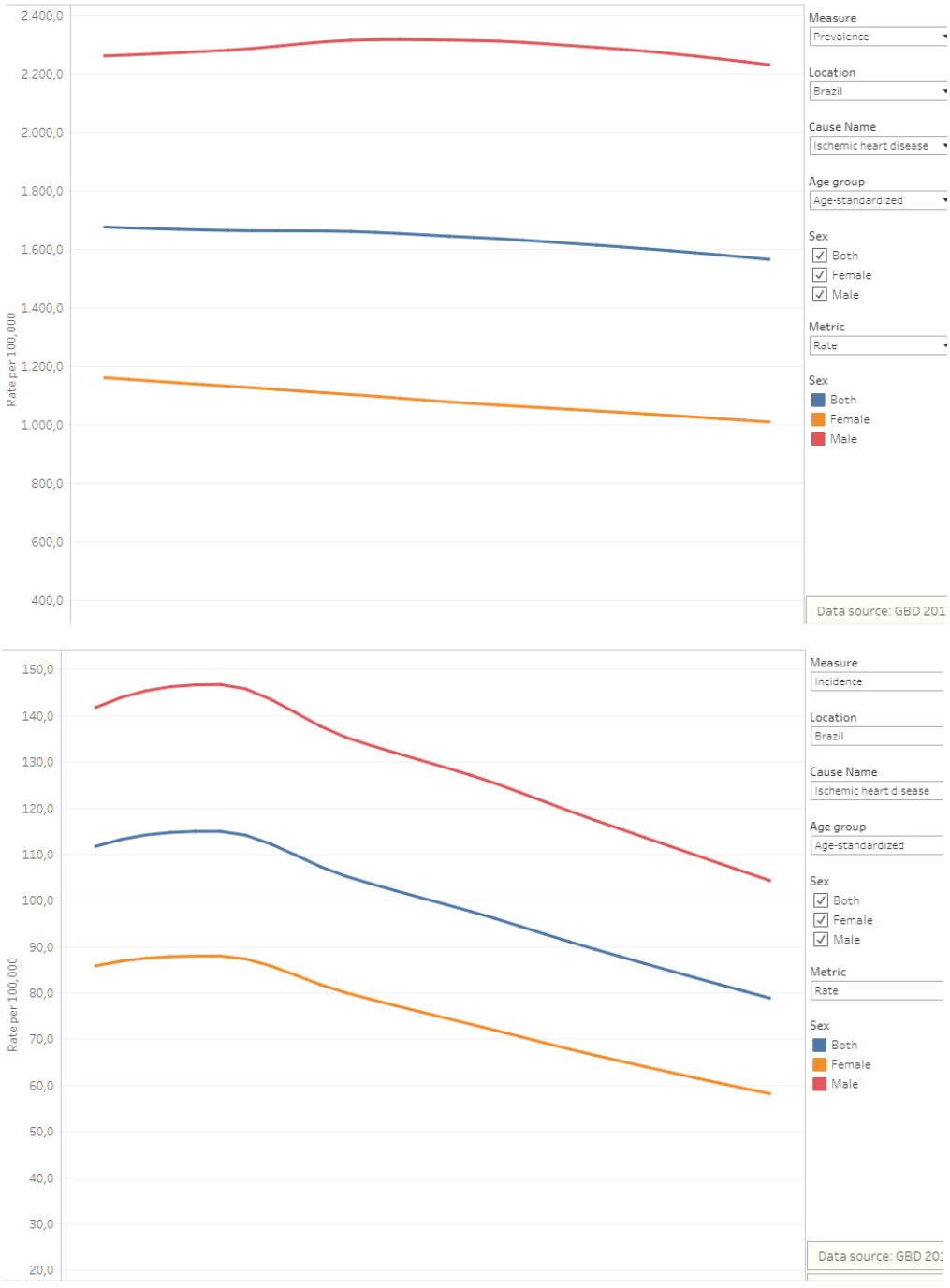


Figure 3 – Age-standardized prevalence (A) and incidence (B) of IHD per 100 000 inhabitants in 2017 and annual percent change from 1990 to 2017, for both sexes.[4]

in 2/3 of the cases, as non-ST-elevation MI (NSTEMI). In addition, MINOCA occurs due to vasospasm of epicardial arteries, associated or not with microcirculation spasm and dysfunction. Vasospasm, as a cause of MI, is rare. It is controversial whether its prevalence is higher in women. However, the presence of coronary spasm in young women has worse prognosis than in older ones. Microcirculation dysfunction is widely accepted in the literature as being more frequent in women and closely related to diabetes mellitus.[9,10]

Two other causes of MINOCA that are more frequent in women are spontaneous coronary dissection and Takotsubo syndrome. Spontaneous dissection is directly related to young women with no risk factor for coronary atherosclerotic disease.[9] It is diagnosed in 10% of women aged <50 years who present with MI, being associated with the peri- and postpartum period, use of oral contraceptives, and connective tissue diseases, mainly fibromyalgia, with a recurrence rate of around 17%, according to Mayo Clinic studies.[10,11] The Takotsubo syndrome is a cardiopathy related to intense physical or emotional stress, being more frequent in older women.[9]

The MI pathophysiologies, other than plaque rupture and erosion, are often underdiagnosed. They should always be in the minds of doctors, who, otherwise, will be at risk of misdiagnosing MI and consequently performing false prognoses when correlating the absence of obstructive coronary disease with an excellent long-term prognosis. Several studies in the literature have shown that patients with ischemia or MINOCA, especially those with microcirculatory dysfunction, have a less favorable prognosis.[11-13]

The correct diagnosis of MI directly influences the patient's prognosis, requiring an adequate perception of the referred symptoms to make the diagnosis as early as possible, allowing the implementation of a treatment capable of favorably changing clinical outcomes. Pain perception is multifactorial and influenced by physiological, anatomical, and psychosocial issues. Women present more frequently with atypical *precordialgia* and pain in the jaw, teeth, throat, back, abdomen and shoulder, in addition to nausea, vomiting, fatigue, and dyspnea.[14]

The population studied can influence the results. Medical reports on the initial presentation of established MI have shown that many women had atypical symptoms leading to an incorrect diagnosis. Because of that, women might have been excluded from the analysis of clinical trials.[13,15]

Risk factors for ischemic heart disease and myocardial infarction

The traditional risk factors for CVD are the same for women and men. However, the differences in the prevalence and impact of these factors vary between genders. Studies point out that women with MI are generally older and have more comorbidities, such as hypertension, dyslipidemia, diabetes, heart failure, and atrial fibrillation. Smoking and diabetes mellitus have a more substantial impact on women. Women <65 years of age with a maternal history of MI are four times more likely to have MI than men of the same age or older women. Young and middle-aged women who smoke have a 25% higher risk of fatal and non-fatal cardiovascular (CV) events.[16]

Women hospitalized with type 1 and type 2 MI have lower socioeconomic status, higher levels of psychosocial disorders, poorer physical/mental health, and lower quality of life than men. Depression, trauma, and stress are powerful predictors of CV risk in young and middle-aged women because of their continuous increase in economic participation and their search for educational achievement.[16]

Early menopause and postmenopause are associated with an adverse risk for CVD. Estrogen has an anti-inflammatory effect and promotes low vascular resistance, protecting premenopause women. Estrogen reduction in menopause has many adverse effects on CV function and metabolism, including changes in body fat distribution, endothelial dysfunction, vascular inflammation, increased sympathetic tone, and increased insulin resistance that contributes to hypertension. However, although initially supported by extensive observational studies, randomized controlled trials have failed to show any CV benefit from menopausal hormone replacement therapy (HRT). They have even demonstrated an increase in MI in postmenopausal women. Thus, the use of HRT for primary and secondary prevention of CVD remains controversial and is currently not recommended.[17]

Iron deficiency is known to increase adverse CV outcomes in women and men. There is a hypothesis that changes in plasma iron levels and metabolism after menopause would negatively affect the CV system due to inflammatory cascade induction.[18] Interestingly, a study has suggested that iron level changes might be an alternative mechanism responsible for the increased risk seen in postmenopausal women. However, the iron hypothesis remains controversial due to the lack of clinical trials to support this thesis.[19]

Pregnancy-related complications are associated with increased CV risk. A recent meta-analysis has concluded that the risk of IHD was higher in women with a history of preeclampsia, placental abruption, gestational hypertension, and diabetes.[20] In addition, the development of gestational diabetes has increased the risk of IHD two to three times up to 25 years after delivery.[21] Pimiparas during

premature delivery (<37 weeks of gestation) had a 1.5-time greater risk of IHD.[22]

These traditional and gender-related risk factors increase female susceptibility to MI and short-term adverse effects after MI. Female gender is a risk factor for bleeding after a percutaneous coronary intervention (PCI). This fact may have contributed to the non-predilection for drug-eluting stents in women. This risk may be even greater among patients at high risk for bleeding. Factors, such as older age and higher prevalence of comorbidities, confer a greater ischemic risk on women. They promote an underutilization of therapies directed to women in MI guidelines.[23] In addition, women with STEMI have an increased risk of bleeding compared to men. Although the female sex may not directly contribute to the increased risk of major adverse cardiac events (MACE), it is associated with comorbidities that increase the risk of ischemic events in the long term.[24]

Clinical and laboratory diagnosis

The risk factors for CVD are similar for both sexes. However, the weight of the risk factors may be different. Data from the INTERHEART Study suggest that 96% of MI risk attributable to the female population occur due to the so-called "modifiable" factors, such as smoking, hypertension, diabetes, obesity, physical activity, alcohol consumption, lipids, and psychosocial factors. Ethnicity is a crucial factor for MI in the female sex because black women have a higher prevalence of MI than the others, including higher cardiac death rates. Asian and Indian women also have higher mortality rates, likely to be associated with higher CVD risk factors. [25,6]

The main symptom that leads to the diagnosis and should trigger treatment initiation in patients with suspected MI is acute chest discomfort, described as pain, pressure, tightness, and burning. Although most patients, including women, have a typical condition, women most often report atypical chest pain or associated symptoms, such as dyspnea, fatigue, sweating, and epigastric pain.[6]

The 12-lead electrocardiogram (ECG) should be performed within 10 minutes after the arrival of the patient with suspected MI to the emergency room, or even in a pre-hospital environment, especially in the search for ST-segment changes.[25] Persistent ST-segment elevation lasting more than 20 minutes should trigger referral for immediate reperfusion by primary PCI or, if not available promptly, by fibrinolytic therapy. Patients with acute chest discomfort but without persistent ST-segment elevation may exhibit transient ST-segment elevation, persistent or transient ST-segment depression, T-wave inversion, flat T waves or T-wave pseudo-normalization; normal ECG is found in approximately 30% of those patients.[25]

Measuring highly sensitive troponin is recommended for all MI patients. However, it is worth noting that many cardiac pathologies, in addition to MI, result in damage to myocardial cells and, therefore, elevations in cardiac troponin. Other biomarkers may be necessary in specific clinical settings when used in combination with the non-highly sensitive troponin T or I. For example, CK-MB shows a faster decline after MI and may assist in the detection of early reinfarction. The initial troponin levels add prognostic information regarding short and long-term mortality to the clinical and ECG variables. In addition, serum creatinine and estimated glomerular filtration rate should be determined in all patients with STEMI because they affect the prognosis and are crucial elements of the GRACE risk score. A GRACE risk score > 140 and dynamic changes in the ST segment recommend an early invasive approach (within 24 hours of admission). [26,27]

Several non-invasive testing techniques may be appropriate in detecting microvascular IHD in women. For high-risk NSTEMI patients, catheterization remains the standard reference approach.[25,26]

An analysis of 68 730 patients enrolled in ten STEMI clinical trials has shown that women have higher rates of all-cause mortality and similar MACE rates.[26] Women with MI should have equal access, immediate diagnosis, and treatments at the same quality and intensity as those offered to male patients. However, these women may receive a higher dose of antithrombotic medication than is appropriate to their weight or kidney function, or both. These may be responsible for the increased risk of in-hospital bleeding complications related to these patients' vascular access. [26,27]

Treatment

Since the 1980s, mortality from MI in women has exceeded that in men.[6] Some studies question the higher MI mortality in women because previous analyses referred to relative mortality, while the most recent trials use standard mortality. Some variables interfere in this MI-related mortality calculation and its associated factors that could disappear when adjusted.[28,29]

Women receive less aggressive drug therapy because they have more associated comorbidities, are older, underdiagnosed, and delay the initial presentation

with lower reperfusion therapy use. After adjusted analysis, there would be no significant differences in mortality between the sexes, decreasing in the STEMI and disappearing or even favoring women in NSTEMI.[29]

Delay in women presenting to medical services to receive initial reperfusion therapy, whether due to thrombolytics or coronary angioplasty, is a challenge to be overcome. Women benefit more than men from primary angioplasty and have a worse prognosis than men when the initial treatment is fibrinolysis.[30] Reports from the GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) Study show that women have more strokes, heart failure, shock, bleeding, recurrent angina, and infarction than men when undergoing thrombolysis.[31]

The study by Alabas et al.[29] assessing mortality from MI in the SWEDEHEART Registry, has shown statistically significant differences between sexes in the application of different therapies. Women received a lesser percentage of reperfusion therapy by both fibrinolysis and angioplasty. The same happens with drug therapy, including aspirin, beta-blockers, statins, P2Y2 inhibitors, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers.[29] These data reinforce the need to intensify the population's and the health team's awareness of the different symptoms in this group to decrease the interval between symptom onset and therapy and improve treatment to achieve the same management percentages indicated in the guidelines for both sexes.

In cases of NSTEMI, early revascularization is also favorable. The elevation of the myocardial necrosis marker is essential for early intervention, which can be more challenging in women. In the study by Slagman et al., troponin has shown a lower positive predictive value in women (53.5%; 95% CI: 42.4–64.3) when compared to men (60.8%; 95% CI: 54.1–67.2) and a slightly higher negative predictive value for women than for men [97.1% (95% CI 96.0–97.9) vs. 96.3% (95% CI 95.2–97.2), respectively].[32]

Women are at higher risk of bleeding when undergoing PCI.[33] Females have a higher prevalence of risk factors calculated in the HAS-BLED (Hypertension, Abnormal renal and liver function, Stroke, Bleeding, Labile INR, Elderly, Drugs, or alcohol) score. Women have a higher incidence of atrial fibrillation during the acute event, requiring oral anticoagulation associated with dual antiplatelet therapy (DAPT) if submitted to intervention with coronary stent, which increases the bleeding risk.[6]

First-generation drug-eluting stents have shown high mortality in women; thus, some studies have preferred to use conventional stents in women. However, state-of-the-art stents and even stents dedicated to patients at high risk of bleeding are superior to previous ones in decreasing MACE in this group.[34]

We must not forget that MINOCA cases require adequate treatment, never inappropriately inferring that the absence of obstructive coronary disease means a better prognosis. Studies on the functional assessment of vascular reactivity and microcirculation dysfunction can identify MI causes and the need for individualized treatment. The CorMicA Trial refers to therapy with nitrates and calcium blockers in vasospasm and beta-blockers, statins, and ACE inhibitors in microcirculatory disorders.[35] In spontaneous coronary dissections, conservative treatment is the first choice, unless hemodynamic instability is present.[36]

Invasive physiological assessment of myocardial infarction in women

The use of physiological assessment as a decision-making method for performing complete revascularization in MI has been supported by the DAMINI 3-PRIMULTI and ACUTE COMPARE trials.[37,38] Both studies have used the fractional flow reserve (FFR) to assess the functional importance of non-culprit artery lesions. The DAMINI 3-PRIMULTI Trial has evaluated the culprit artery 48 hours after the acute event and primary angioplasty. The ACUTE COMPARE Trial has performed the functional evaluation in the same primary angioplasty procedure. Compared with the angioplasty of the culprit artery alone, both studies have shown decreased subsequent revascularizations when using the FFR, with no decrease in hard outcomes, such as death and infarction. The COMPLETE Trial, comparing complete angiography-guided revascularization versus target-lesion revascularization, has shown a reduction in death and MI in a 3-year follow-up.[39]

The FFR use in MI requires normal microcirculation to react with maximum hyperemia after vasodilator.[40] Although the instantaneous wave-free ratio (iFR) does not dependent on the microcirculation and does not require a vasodilator, it has not been evaluated in the MI scenario. An FFR <0.80 suggests the need for revascularization, and an FFR > 0.80 may be overestimated because of the inadequate response to microcirculation vasodilation in MI due to a decrease in

the gradient between pre- and post-stenosis pressures. (Figure 4).[40]

The impact of that analysis is more significant when MI occurs in women, because they have a higher prevalence of microcirculatory dysfunction. Women have been proven to have higher mean FFR than men.[6,41] A recent study assessing the microcirculation situation in the non-culprit vessel during the acute event, even with small sampling and 80% being male, has found 93% of patients with some degree of dysfunction and only 34% of abnormal FFR.[42]

It is worth noting that plaque erosion occurs significantly more often in women in association of higher frequency of distal microembolization that mechanically impacts microcirculation.[6] So far, there has been no certainty as to how long after MI normalization of the microcirculation occurs. Because it is often a mechanical phenomenon and not exclusively metabolic, the period required to return to normality may be much longer than a few days.

Thus, whenever the FFR > 0.80 at any time during the acute or subacute phase of MI, the functional assessment of the microcirculation, using a specific index for that, would be ideal. The indices of functional assessment of the microcirculation, such as coronary flow reserve and hyperemic microcirculation ratio, are essential but little used in clinical practice because of their complexity. On the other hand, the index of microvascular resistance, performed by using thermodilution, is easy to use in catheterization laboratories, reproducible and reliable, being identified as a predictor of clinical outcomes in the CORMICA Trial.[43,44]

Considering the pathophysiology of MI in women, the research of vascular reactivity of both macro and micro coronary circulations can identify vasospastic phenomena as causing the acute event. The use of intravenous or intracoronary acetylcholine with evidence of significant spasm of coronary epicardial vessels guides us to diagnose macrovascular spasm. In contrast, the presence of angina symptoms and evidence of ischemia, in the absence of epicardial coronary vasospasm, lead us to the probable diagnosis of microvascular spasm.[43]

In conclusion, the use of invasive physiological assessment in women with MI should be carefully

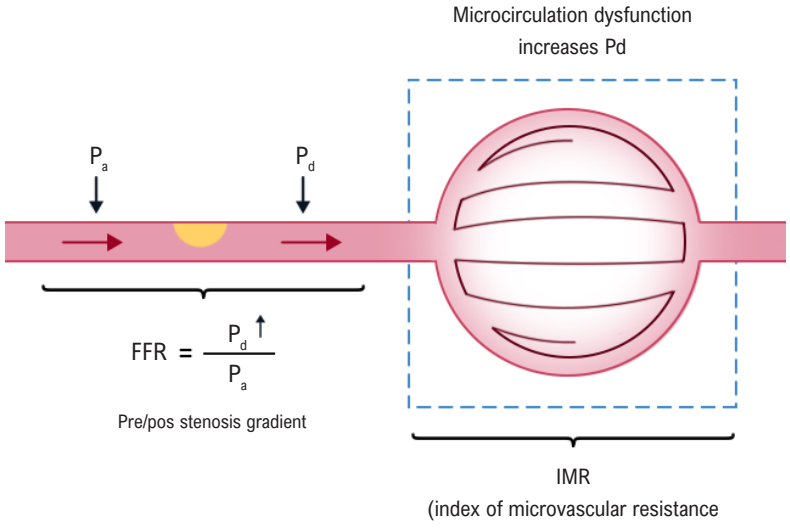


Figure 4 – Representation of an epicardial vessel with stenosis (yellow) and microcirculation distal to the lesion. Fractional flow reserve (FFR) analysis assesses the difference between pre-stenosis pressure (Pa = aortic pressure) and post-stenosis pressure (Pd = distal pressure). While FFR is an index to assess only lesions in epicardial vessels, the index of microvascular resistance (IMR) is only for microcirculatory assessment. In the presence of dysfunction of the microcirculation, the IMR increases. It can be easily seen that the microcirculatory dysfunction interferes in the velocity of blood flow distal to the epicardial lesion, increasing Pd. With this elevation in the numerator of the fraction 'Pd/Pa', FFR is overestimated.[40]

analyzed, never considering the investigation completed if FFR >0.80, requiring associated diagnostic tests.

Percutaneous invasive treatment

Women and young people are more likely to have normal coronary arteries or mild irregularities, diffuse disease, single-vessel disease, or other angiographic findings, such as coronary dissection, when facing MI. The CASS trial, comparing angiographic results in young men and women, has observed frequent normal coronary arteries in young women.[45-50] Moreover, having MI symptoms with normal coronary arteries, about 20% of young women will have myocardial ischemia, probably due to microcirculation involvement.[51-54]

There is an established benefit for men using an early invasive strategy for NSTEMI and revascularization, if applicable. However, among women, this strategy has specific nuances. Contemporary meta-analysis has shown that, for men, the early invasive approach improves survival. However, for women, the benefit is more significant in the population with an elevation of troponin markers (OR 0.47, 95% CI: 0.26-0.83). [47] A subsequent meta-analysis involving 3000 women and 7000 men has corroborated that same concept, but it has not occurred in low-risk women with negative biomarkers. [47]

In general, even more recently, the routine of treating women less aggressively in the presence of STEMI has persisted. A recent review based on CRUSADE with approximately 36 000 patients, 41% of whom were women, has found that this group was treated less aggressively than men. In a lower percentage, women underwent cardiac catheterization within 24 hours of admission (42% x 49% among men). Consequently, they had a lower percutaneous treatment rate simultaneously (44% x 52% for men). [46]

Data obtained from two major academic health systems in the United States between 2000 and 2016 demonstrated that a lower percentage of women under 50 years of age affected by MI were submitted to coronary revascularization (82.1% against 92.6% among men, p <0.001). [48]

In STEMI, women undergoing primary angioplasty have a higher risk of in-hospital and late mortality, perhaps because they are older and have more comorbidities, which have also been found in the CADILLAC trial. At the end of 1 year after MI, women have significantly higher rates of mortality (7.6 x 3% among men), target-vessel revascularization (16.7 x12.1%), and major adverse events (23.9 x 15.3 for men).[49] These differences are due to their higher prevalence of risk factors, such as diabetes, hypertension, and kidney failure, their lower body surface area, and the use of drugs, such as anticoagulants, without adjustment to weight.[49,50] However, after adjustments, the female gender was not a risk factor for mortality in the CADILLAC trial.

It is important to note that women have a higher ischemic risk and a higher risk of sex-related bleeding. Biological factors linked to the female gender may hinder DAPT, and they should be included in the bleeding scores. In addition, women are underrepresented in studies involving DAPT because of sex-related factors and cultural and socioeconomic characteristics.[55] The higher risk of bleeding and the early cessation of DAPT, coupled with elevated ischemic risk in women, increase the worst results after PCI and hinder PCI performance. [23,24,56]

Clinical implications

This review highlights the sex and gender influences that exist for IHD and MI. Figures 5 and 6 summarize the main points.

Ischemic heart disease and heart failure with preserved ejection fraction due to IHD are significant contributors to heart disease mortality in women. Of note, systolic blood pressure and hypertension, smoking, and diabetes are associated with higher hazard ratios for MI in women than in men.[56]

In addition, a study has reported that women with MI treated by male emergency doctors have a higher mortality rate than those treated by female emergency doctors. The MI approach is more effective when female patients are treated by female doctors.[57]

In conclusion, sex influences disease pathophysiology, clinical presentation, response to treatment, clinicians' behavior, and how and when patients have access to health care. Precision medicine must consider sex and age at a high decision level to promote correct IHD and MI diagnosis, as well as treatment and gender equity in health care. [56]

Author contributions

Conception and design of the research: Ferreira MCMF, Oliveira MV, Oliveira GMM. Acquisition of data: Ferreira MCMF, Oliveira MV, Paiva MSM, Lemke V, Mangione F, Oliveira GMM. Analysis and interpretation

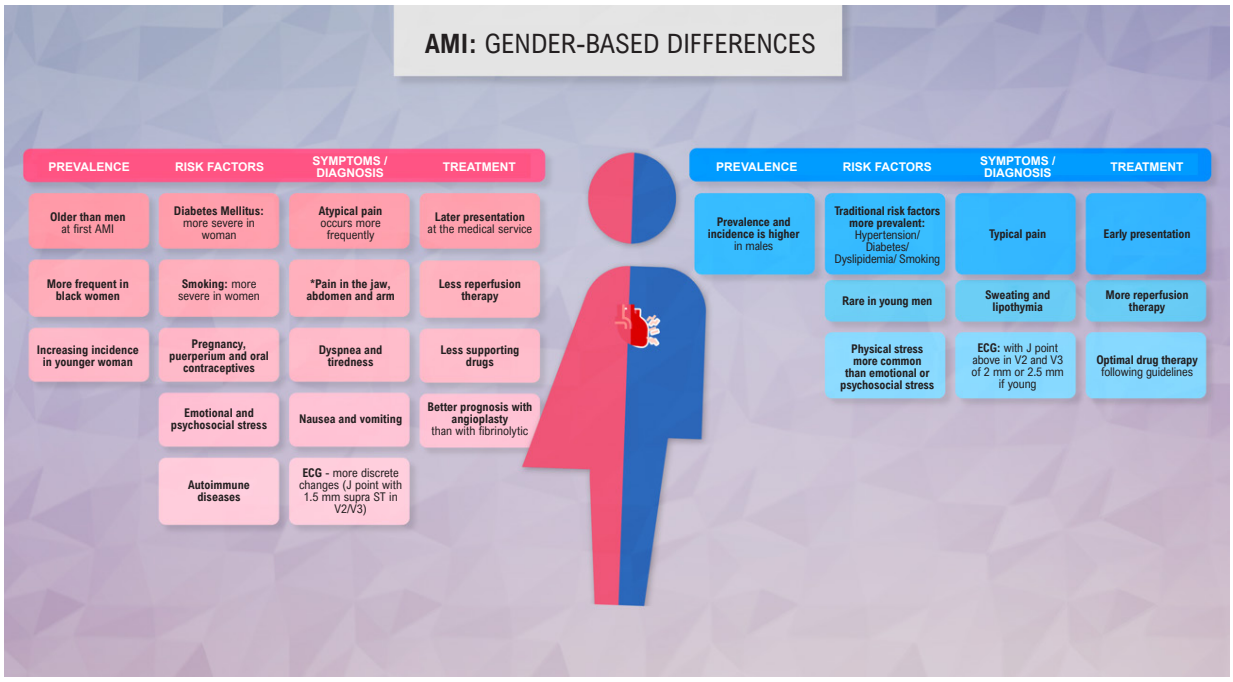


Figure 5 – Sex-based differences in prevalence, risk factors, symptoms, diagnosis, and treatment.[6, 16, 55] MI: myocardial infarction; ECG: electrocardiogram; FFR: fractional flow reserve.

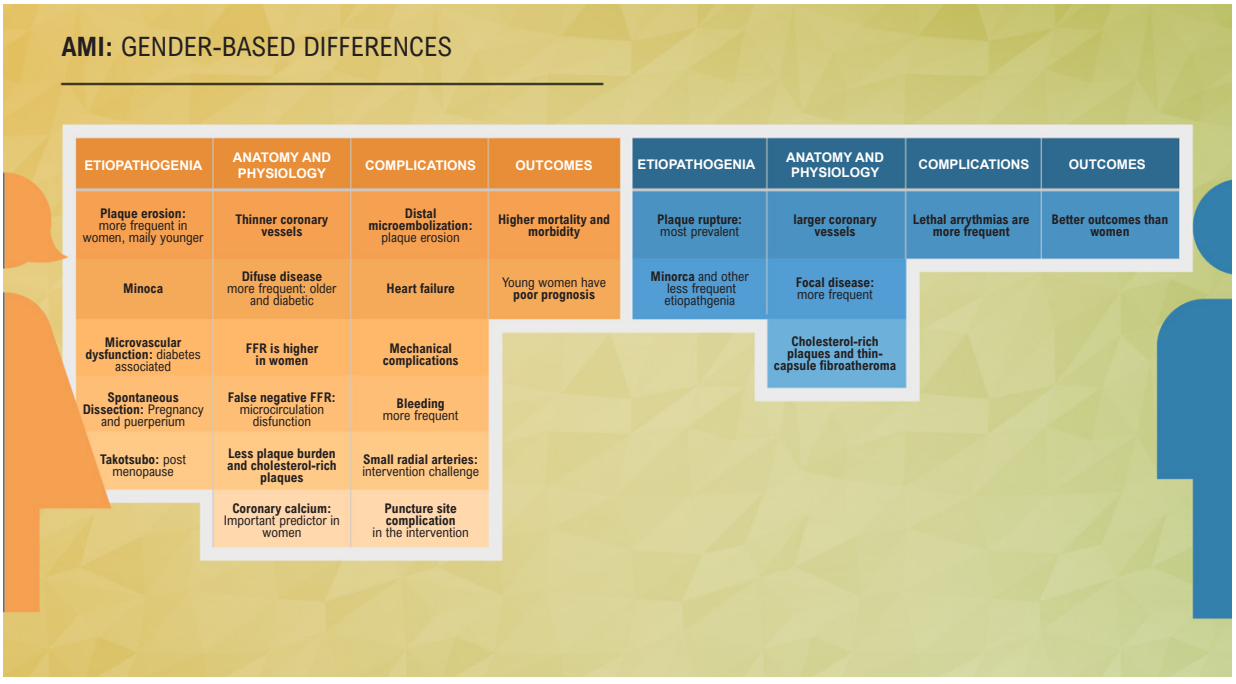


Figure 6 – Sex-based differences in etiopathogenesis, anatomy, physiology, complication, and outcomes.[6,16] MI: myocardial infarction; MINOCA: myocardial infarction with nonobstructive coronary arteries; FFR: fractional flow reserve.

of the data: Ferreira MCMF, Oliveira MV, Paiva MSM, Lemke V, Mangione F, Oliveira GMM. Writing of the manuscript: Ferreira MCMF, Paiva MSM, Lemke V, Mangione F, Oliveira GMM. Critical revision of the manuscript for intellectual content: Ferreira MCMF, Oliveira MV, Oliveira GMM.

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. Schultz WM, Kelli HM, Lisko JC, Varghese T, Shen J, Sandesara P, et al. Socioeconomic Status and Cardiovascular Outcomes: Challenges and Interventions. Circulation 2018; 137(20): 2166–2178.
2. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019 Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(22):2982-3021.
3. Institute for Health Metrics and Evaluation (IHME). GBD Compare | Viz Hub. Disponível em: https://vizhub.healthdata.org/gbd-compare/ (Internet) [Citado em 22 dezembro, 2020].
4. Oliveira GMM, Brant LCC, Polanczyk, CA, Biolo A, Nascimento BR. Malta DC. Estatística Cardiovascular – Brasil 2020. Arq Bras Cardiol. 2020; 115(3):308-439.
5. Brasil. Ministerio da Saúde. DATASUS: Informações de Saúde, Morbidade e Informações Epidemiológicas [Internet]. Brasília: Ministério da Saúde Brasil. 2019 - [cited 2020 feb 3]. Avaible from: http://datasus.saude.gov.br/informacoes-de-saude/tabnet/epidemiologicas-e-morbidade.
6. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN, et al. American Heart Association Cardiovascular Disease in Women and Special Populations Committee of the Council on Clinical Cardiology, Council on Epidemiology and Prevention, Council on Cardiovascular and Stroke Nursing, and Council on Quality of Care and Outcomes Research. Acute Myocardial Infarction in Women: A Scientific Statement From the American Heart Association. Circulation. 2016 Mar 1; 133 (9): 916-47.
7. Kawamoto KR, Davis MB, Duvernoy CS. Acute Coronary Syndromes: Differences between Men and Women. Curr Atheroscler Rep. 2016 Dec; 18 (12): 73.
8. Safdar B, Spatz ES, Dreyer RP, Beltrame JF, Lichtman JH, Spertus JA, et al. Presentation, clinical profile, and prognosis of young patients with myocardial infection with non-obstructive coronary arteries (MINOCA): results from the VIRGO study. J Am Heart Assoc. 2018 Jun 28;7(13):e009174.
9. Pustjens TFS, Appelman Y, Damman P, Ten Berg JM, Jukema JW, de Winter RJ, et al. Guidelines for managing myocardial infarction/injury with non-obstructive coronary arteries (MINOCA): a position paper from the Dutch ACS working group. Neth Heart J. 2020 Mar; 28 (3): 116-130.
10. Hayes SN, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, et al. American Heart Association Council on Peripheral Vascular Disease; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Genomic and Precision Medicine; and Stroke Council. Spontaneous Coronary Artery Dissection: Current State of the Science: A Scientific Statement From the American Heart Association. Circulation. 2018 May 8; 137 (19): e523-e557.
11. Tweet MS, Hayes SN, Pitta SR, Simari RD, Lerman A, Lennon RJ, et al. Clinical features, management, and prognosis of spontaneous coronary artery dissection. Circulation. 2012; 126: 579–588.
12. Malmborg M, Schmiegelow MDS, Nørgaard CH, Munch A, Gerds T, Schou M, et al. Does type 2 diabetes confer higher relative rates of cardiovascular events in women compared with men? Eur Heart J. 2020 Apr 1; 41 (13): 1346-1353.
13. Devon HA, Rosenfeld A, Steffen AD, Daya M. Sensitivity, specificity, and sex differences in symptoms reported on the 13-item acute coronary syndrome checklist. J Am Heart Assoc. 2014; 3 (2): e000586.
14. Lovlien M, Schei B, Gjengedal E. Are there gender differences related to acute myocardial infarction symptoms? Norwegian perspective. Prog Cardiovasc Nurs. 2006 Winter; 21 (1): 14-9.
15. Arora G, Bittner V. Chest pain characteristics and gender in the early diagnosis of acute myocardial infarction. Curr Cardiol Rep. 2015 Feb; 17 (2): 5.
16. Haider A; Bengs S, Luu J, Osto E, Siller-Matula J M, Muka Ta, Gebhard C. Sex and gender in cardiovascular medicine: presentation and outcomes of an acute coronary syndrome. European Heart Journal (2019) 0, 1–14 doi:10.1093/eurheartj/ehz898.
17. Rosano GM, Vitale C, Marazzi G, Volterrani M. Menopause, and cardiovascular disease: the evidence. Climacteric 2007;10(Suppl 1):19–24.
18. Manson JE, Hsia J, Johnson KC, Rossouw JE, Assaf AR, Lasser NL, et al. Estrogen plus progestin and the risk of coronary heart disease. N Engl J Med 2003; 349:523–534.
19. Muka T, Chowdhury R, Franco OH. Effect of iron levels on women after premature or early-onset menopause-reply. JAMA Cardiol 2017; 2:458–459.
20. Rich-Edwards JW, Fraser A, Lawlor DA, Catov JM. Pregnancy characteristics and women's future cardiovascular health: an underused opportunity to improve women's health? Epidemiol Rev 2014; 36:57–70.
21. Grandi SM, Filion KB, Yoon S, Ayele HT, Doyle CM, Hutcheon JA, et al. Cardiovascular disease-related morbidity and mortality in women with a history of pregnancy complications. Circulation, 2019;139:1069–1079.
22. Tanz LJ, Stuart JJ, Williams PL, Rimm EB, Missmer SA, Rexrode KM, Mukamal KJ, Rich-Edwards JW. Preterm delivery and maternal cardiovascular disease in young and middle-aged adult women. Circulation, 2017;135:578–589.
23. Chandiramani R, Mehran R. Sex-Related Differences in Patients at High Bleeding Risk Undergoing Percutaneous Coronary Intervention: A Patient-Level Pooled Analysis From 4 Postapproval Studies. J Am Heart Assoc 2020 Apr 7;9(7): e014611.

24. Yu J, Mehran R, Grinfeld L, Xu K, Nikolsky E, Brodie B, et al. Sex-based differences in bleeding and long term adverse events after percutaneous coronary intervention for acute myocardial infarction: three-year results from the HORIZONS-AMI trial Catheter. Cardiovasc Interv. 2015 Feb 15;85(3):359-68.

25. Collet JP, Thiele Holger, Barbato E, Barthélémy O, Bauersachs J, L Bhatt D, et al. ESC Scientific Document Group, 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment 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), European Heart Journal, ehaa575, https://doi.org/10.1093/eurheartj/ehaa575.

26. Sarma AA, Braunwald E, Cannon CP, Guo J, KyungAh Im, Antman EM, et al. Outcomes of Women Compared With Men After Non–ST-Segment Elevation Acute Coronary Syndromes. J Am Coll Cardiol. 2019 Dec, 74 (24) 3013–3022.

27. Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. Grupo de Documentos Científicos da ESC, Diretrizes da ESC / EACTS sobre revascularização do miocárdio, European Heart Journal , Volume 40 , Edição 2, 07 de janeiro de 2019, páginas 87-165, https://doi.org/10.1093/eurheartj/ehy394.

28. Redfors B, Angerås O, Råmunddal T, Petursson P, Haraldsson I, Dworeck C, et al. Trends in Gender Differences in Cardiac Care and Outcome After Acute Myocardial Infarction in Western Sweden: A Report From the Swedish Web System for Enhancement of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDEHEART). J Am Heart Assoc. 2015 Jul 14; 4 (7): e001995.

29. Alabas OA, Gale CP, Hall M, Rutherford MJ, Szummer K, Lawesson SS, Alfredsson J, Lindahl B, Jernberg T. Sex Differences in Treatments, Relative Survival, and Excess Mortality Following Acute Myocardial Infarction: National Cohort Study Using the SWEDEHEART Registry. J Am Heart Assoc. 2017 Dec 14; 6 (12): e007123.

30. Kawamoto KR, Davis, MB, Duvernoy CS. Acute Coronary Syndromes: Differences in Men and Women. Curr Atheroscler Rep. 2016 Dec; 18 (12): 73.

31. Lee KL, Califf RM, Simes J, Van de Werf F, Topol EJ. Holding GUSTO up to the light. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. Ann Intern Med. 1994 May 15; 120 (10): 876-81; discussion 882-5.

32. Slagman A, Searle J, Vollert JO, Storchmann H, Buschenfelde DM, von Recum J, et al. Sex differences of troponin test performance in chest pain patients. Int J Cardiol. 2015; 187: 246–51.

33. Chandiramani R, Cao D, Claessen BE, Sorrentino S, Guedeney P, Blum M, et al. Sex-Related Differences in Patients at High Bleeding Risk Undergoing Percutaneous Coronary Intervention: A Patient-Level Pooled Analysis From 4 Postapproval Studies. J Am Heart Assoc. 2020 Apr 7; 9 (7): e014611.

34. Stefanini GG, Baber U, Windecker S, Morice MC, Sartori S, Leon MB, et al. Safety and efficacy of drug-eluting stents in women: a patient-level pooled analysis of randomized triples. Lancet. 2013; 382: 1878].

35. Ford TJ, Stanley B, Good R, Rocchiccioli P, McEntegart M, Watkins S, et al. Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina: The CorMicA Trial. J Am Coll Cardiol. 2018 Dec 11; 72 (23 Pt A): 2841-2855.

36. Hayes SN, Kim ESH, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, et al; American Heart Association Council on Peripheral Vascular Disease; Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Genomic and Precision Medicine; and Stroke Council. Spontaneous Coronary Artery Dissection: Current State of the Science: A Scientific Statement From the American Heart Association. Circulation. 2018 May 8; 137 (19): e523-e557.

37. Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, et al. DANAMI-3 — PRIMULTI Investigators. Complete revascularization versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3 — PRIMULTI): an open-label, randomized controlled trial. Lancet. 2015 Aug 15; 386 (9994): 665-71.

38. Smits PC, Abdel-Wahab M, Neumann FJ, Boxma-de Klerk BM, Lunde K, Schotborgh CE, et al. Fractional Flow Reserve-Guided Multivessel Angioplasty in Myocardial Infarction. N Engl J Med. 2017 Mar 30; 376 (13): 1234-1244.

39. Mehta SR, Wood DA, Storey RF, Mehran R, Bainey KR, Nguyen H, et al. COMPLETE Trial Steering Committee and Investigators. Complete Revascularization with Multivessel PCI for Myocardial Infarction. N Engl J Med. 2019 Oct 10; 381 (15): 1411-1421.

40. Liou KP, Ooi SM, Hoole SP, West NEJ. Fractional flow reserve in acute coronary syndrome: a meta-analysis and systematic review. Open Heart. 2019 Jan 13; 6 (1): e000934.

41. Kim CH, Koo BK, Dehbi HM, Lee JM, Doh JH, Nam CW, et al. Sex Differences in Instantaneous wave-free Ratio or Fractional Flow Reserve-Guided Revascularization Strategy. JACC Cardiovasc Interv. 2019 Oct 28; 12 (20): 2035-2046.

42. Díez-Delhoyo F, Gutiérrez-Ibañes E, Sanz-Ruiz R, Vázquez-Álvarez ME, González Saldívar H, Rivera Juárez A, et al. Prevalence of Microvascular and Endothelial Dysfunction in the Nonculprit Territory in Patients With Acute Myocardial Infarction. Circ Cardiovasc Interv. 2019 Feb; 12 (2): e007257.

43. Ford TJ, Stanley B, Good R, Rocchiccioli P, McEntegart M, Watkins S. Stratified Medical Therapy Using Invasive Coronary Function Testing in Angina: The CorMicA Trial. J Am Coll Cardiol. 2018 Dec 11; 72 (23 Pt A): 2841-2855.

44. Tamis-Holland JE, Jneid H, Reynolds HR, Agewall S, Brilakis ES, Brown TM, et al. American Heart Association Interventional Cardiovascular Care Committee of the Council on Clinical Cardiology; Council on Cardiovascular and Stroke Nursing; Council on Epidemiology and Prevention; and Council on Quality of Care and Outcomes Research. Contemporary Diagnosis and Management of Patients With Myocardial Infarction in the Absence of Obstructive Coronary Artery Disease: A Scientific Statement From the American Heart Association. Circulation. 2019 Apr 30; 139 (18): e891-e908.

45. Lee PY, Alexander KP, Hammill BG, Pasquali SK, Peterson ED. Representation of elderly persons and women in published randomized trials of acute coronary syndromes. JAMA 2001; 286:708.

46. Kim ES, Carrigan TP, Menon V. Enrollment of women in National Heart, Lung, and Blood Institute-funded cardiovascular randomized controlled trials fails to meet current federal mandates for inclusion. J Am Coll Cardiol 2008; 52:672.

47. O'Donoghue M, Boden WE, Braunwald E, Cannon CP, Clayton TC, Winter RJ, et al. Early invasive vs conservative treatment strategies in women and men with unstable angina and non-ST-segment elevation myocardial infarction: a meta-analysis. JAMA 2008; 300:71.

48. DeFilippis EM, Collins BL, Singh A, Biery DW, Fatima A, Qamar A, et al. Women who experience a myocardial infarction at a young age have worse outcomes compared with men: the Mass General Brigham YOUNG-MI registry. Eur Heart J 2020; 41:4127.

49. Antoniucci D, Valenti R, Moschi G, Migliorini A, Trapani M, Santoro GM, Bolognese, Dovellini EV, et al. Sex-based differences in clinical and angiographic outcomes after primary angioplasty or stenting for acute myocardial infarction. Am J Cardiol 2001; 87:289.

50. Stone GW, Grines CL, Browne KF, Marco J, Rothbaum D, O'Keefe J, et al. Comparison of in-hospital outcome in men versus women treated by either thrombolytic therapy or primary coronary angioplasty for acute myocardial infarction. Am J Cardiol 1995; 75:987.

51. Sullivan AK, Holdright DR, Wright CA, Sparrow JL, Cunningham D, Fox KM, et al. Chest pain in women: clinical, investigative, and prognostic features. BMJ 1994; 308:883.

52. Gurevitz O, Jonas M, Boyko V, Rabinowitz B, Reicher-Reiss H. Clinical profile and long-term prognosis of women < or = 50 years of age referred for coronary angiography for evaluation of chest pain. Am J Cardiol 2000; 85:806.

53. Buchthal SD, den Hollander JA, Bairey Merz CN, Rogers WJ, Pepine CJ, Reichek N, et al. Abnormal myocardial phosphorus-31 nuclear magnetic resonance spectroscopy in women with chest pain but normal coronary angiograms. N Engl J Med 2000; 342:829.

54. Johnson BD, Shaw LJ, Buchthal SD, Merz Bairey CN, Kim HW , Scott KN, et al. Prognosis in women with myocardial ischemia in the absence of obstructive coronary disease: results from the National Institutes of Health-National Heart, Lung, and Blood Institute-Sponsored Women's Ischemia Syndrome Evaluation (WISE). Circulation 2004; 109:2993.

55. Mehta LS, Beckie TM, DeVon HA, Grines CL, Krumholz HM, Johnson MN et al. Acute Myocardial Infarction in Women: A Scientific Statement from the American Heart Association. Circulation. 2016 Mar 1;133(9):916-47 3- Thygesen K, et al. Fourth Universal Definition of Myocardial Infarction (2018). Circulation. 2018 Nov 13;138(20):e618-e651.

56. Mauvais-Jarvis F, Merz NB, Barnes PJ, Brinton RD, Carrero JJ, DeMeo DL, et al. sex and gender: modifiers of health, disease, and medicine. Lancet 2020; 396: 565–82

57. Greenwood BN, Carnahan S, Huang L. Patient-physician gender concordance and increased mortality among female heart attack patients. Proc Natl Acad Sci USA 2018; 115: 8569–74.

Int J Cardiovasc Sci. 2021; 34(4):484-485

EDITORIAL

How the Gender Gap Affects the Incidence and Prognosis of Cardiovascular Disease

Maria Gazzilli[1]

Nuclear Medicine - University of Brescia and Spedali Civili Brescia,[1] Brescia – Italy

Editorial Referring to the article: Closing the Gender Gap in Ischemic Heart Disease and Myocardial Infarction

The study in this issue of the Journal analyzed the sex and gender gap that exists for ischemic heart disease and myocardial infarction. The authors reviewed all the factors that differ between genders in terms of incidence, mortality, pathophysiology and clinical implications, diagnosis, and treatment.[1]

The article highlights firstly that there has been an increase in the annual change in proportional mortality from ischemic heart disease in women in recent years, with an age-standardized incidence of 104 per 100 000 population for males and 58 per 100 000 population for females.[2-3]

Although it is well known that there are important differences between men and women in the prevalence of risk factors for cardiovascular disease (CVD), studies have focused attention on older women with more comorbidities such as hypertension, dyslipidemia, diabetes, heart failure, and atrial fibrillation, demonstrating that smoking and diabetes mellitus have a more substantial impact on women. Moreover, postmenopausal hormonal changes play an important role in women's CVD.[4-5]

Further differences between men and women become apparent when considering the less common etiologies of cardiomyopathy. In fact, myocardial infarction with nonobstructive coronary arteries (MINOCA) is five times more likely to occur in women than in men as demonstrated by the VIRGO study.[6]

MINOCA occurs due to epicardial artery vasospasm, spontaneous coronary artery dissection, and Takotsubo syndrome, the last two conditions are common in young women. Tweet et al.[7] demonstrated that patients with MINOCA, especially women with microcirculatory dysfunction, had a poor prognosis related also to atypical symptoms, such as atypical chest pain, or associated symptoms, such as dyspnea, fatigue, sweating, and epigastric pain, thus leading to an incorrect diagnosis.

These differences in pathophysiology, clinical presentation and risk factors affect prognosis and treatment. The GUSTO study[8] showed how women benefit more than men from primary angioplasty and have a poorer prognosis when fibrinolysis is the initial treatment of choice, because women have more strokes, heart failure, shock, bleeding, recurrent angina, and infarction than men when undergoing thrombolysis.

Furthermore, in non-ST elevation myocardial infarction (NSTEMI), although early revascularization is favorable, the elevated marker of myocardial necrosis is a challenge in women. Slagman et al.[9] demonstrated that troponin had a lower positive predictive value and a slightly higher negative predictive value in women than in men.

As demonstrated by the DANAMI-3—PRIMULTI[10] and Acute Compare trials, fractional flow reserve (FFR) is fundamental to the decision-making for revascularization; in fact, according to these studies, an FFR < 0.80 suggests the need for revascularization, but the impact of this analysis is more significant when myocardial infarction occurs in women because they

Keywords

Ischemic Heart Disease; Myocardial infarction.

Maria Gazzilli, MD
Nuclear Medicine
ASST Spedali Civili of Brescia (Italy)

Mailing Address: Maria Gazzilli
Piazzale Spedali Civili, 1. Postal Code: 25123, Brescia – Italy.
E-mail: marinagazzilli@msn.com

DOI: https://doi.org/10.36660/ijcs.20210132

have a higher prevalence of microcirculatory dysfunction than men. In women, it is essential to consider the use of a functional assessment index of the microcirculation such as coronary flow reserve (CFR) and hyperemic microvascular resistance (HMR).

I invite you to read this article to understand all the mechanisms behind the gender gap in CVD and to discover how precision medicine must consider sex and age at a high level of decision-making to reach the correct diagnosis and treatment in CVD.

References

1. Ferreira MCM, Oliveira MV, Paiva MSM, Lemke V, Mangione F, Oliveira GMM. Closing the Gender Gap in Ischemic Heart Diseases and Myocardial Infarction. Int J Cardiovasc Sci. 2021; 34(4):471-483 doi: https://doi.org/10.36660/ijcs.20210001
2. Global Burden of Disease Study 2019 (GBD 2019) results. Global Health Data Exchange website. Seattle, WA: Institute for Health Metrics and Evaluation (IHME), University of Washington; 2019.
3. Oliveira GMM, Brant LCC, Polanczyk CA, Biolo A, Nascimento BR, Malta DC, et al. Cardiovascular statistics - Brazil 2020. Arq Bras Cardiol. 2020;115(3):308-439. doi: 10.36660/abc.20200812.
4. Haider A, Bengs S, Luu J, Osto E, Siller-Matula JM, Muka T, et al. Sex and gender in cardiovascular medicine: presentation and outcomes of acute coronary syndrome. Eur Heart J. 2020;41(13):1328-36. doi: 10.1093/eurheartj/ehz898.
5. Rosano GM, Vitale C, Marazzi G, Volterrani M. Menopause and cardiovascular disease: the evidence. Climacteric. 2007;(10 Suppl 1):19-24. doi: 10.1080/13697130601114917.
6. Safdar B, Spatz ES, 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. J Am Heart Assoc. 2018;7(13):e009174. doi: 10.1161/JAHA.118.009174.
7. Tweet MS, Hayes SN, Pitta SR, Simari RD, Lerman A, Lennon RJ, et al. Clinical features, management, and prognosis of spontaneous coronary artery dissection. Circulation. 2012;126(5):579-88. doi: 10.1161/CIRCULATIONAHA.112.105718.
8. Lee KL, Califf RM, Simes J, Van de Werf F, Topol EJ. Holding GUSTO up to the light. Global utilization of streptokinase and tissue Plasminogen activator for occluded coronary arteries. Ann Intern Med. 1994;120(10):876-81; doi: 10.7326/0003-4819-120-10-199405150-00009.
9. Slagman A, Searle J, Vollert JO, Storchmann H, Büschenfelde DM, von Recum J, et al. Sex differences of troponin test performance in chest pain patients. Int J Cardiol. 2015;187:246-51. doi: 10.1016/j.ijcard.2015.03.261.
10. Engstrøm T, Kelbæk H, Helqvist S, Høfsten DE, Kløvgaard L, Holmvang L, et al. Complete revascularisation versus treatment of the culprit lesion only in patients with ST-segment elevation myocardial infarction and multivessel disease (DANAMI-3—PRIMULTI): an open-label, randomised controlled trial. Lancet. 2015;386(9994):665-71. doi: 10.1016/s0140-6736(15)60648-1.

Int J Cardiovasc Sci. 2021; 34(4):486-489

CASE REPORT

Linear and Nonlinear Heart Rate Variability Analysis in Gonadal Dysgenesis (Swyer Syndrome): A Case Report

Valdelias Xavier Pereira,[1] Tatiana Dias de Carvalho,[2] Marcos Antonio Marinovic Junior,[1] Alex Rey Norberto,[1] José Maria Soares Júnior,[1] Vitor Engrácia Valenti,[3] Isabel Cristina Esposito Sorpreso[1]

Faculdade de Medicina da Universidade de São Paulo,[1] São Paulo, SP – Brazil
Universidad Nacional de La Matanza,[2] San Justo, Buenos Aires – Argentina
Universidade Estadual Paulista,[3] São Paulo, SP – Brazil

Abstract

Swyer syndrome is one of the disorders of sexual differentiation. Previous studies have demonstrated increased sympathetic activity with heart rate variability (HRV) analysis with decreasing estradiol levels. One patient presented a pure 46, XY gonadal dysgenesis with female phenotype. Cardiac autonomic modulation was assessed through HRV analysis while at rest. This research analyzed linear and nonlinear indexes. HRV analysis showed reduced parasympathetic and global modulation with an apparent increase in sympathetic tone and a loss of HR fractal dynamics toward correlated behavior, characterized by low entropy and high determinism of time series.

Introduction

Swyer syndrome is one of the disorders of sexual differentiation (DSD), a pure gonadal dysgenesis with karyotype 46, XY, the presence of two digenetic gonads or gonads streak. and devoid of germinative elements. The clinical presentations are female phenotype with typical female external genitalia, primary amenorrhea and persistent hypergonadotropic hypogonadism, normal stature, and absence of somatic malformations.[1]

Previous studies have demonstrated increased sympathetic activity with heart rate variability (HRV) analysis with decreasing estradiol levels. However, the clinical and therapeutic implication of autonomic impairment is still unclear.[1] This study reports on the autonomic behavior of HRV in Swyer Syndrome, but the report exempts itself from an in-depth review.

Keywords

Autonomic Nervous System; Estrogen, Replacement Therapy; Amenorrhea; Gonadectomy; Heart Rate; Cardiovascular Diseases/complications.

Case Report

A 48-year-old married Brazilian woman participated in this research in the Endocrine Gynecology and Menopause Clinic the São Paulo University Medical School. Patient follow-up began in 1983, at which time the patient received a diagnosis of gonadal dysgenesis in her adolescence. This case report was approved by the ethics committee of the *Faculdade de Medicina da Universidade de São Paulo* (FMUSP) (Protocol n° 2.368.076), and the patient's anonymity and consent were guaranteed.

After the primary amenorrhea diagnosis, followed by the gonadal dysgenesis diagnosis, the patient was treated with estradiol valerate and levonorgestrel (2mg+ 0.25mg)/day. At age 21, she went through a bilateral oophorectomy procedure. She reported no other hospitalizations, pre-existing diseases, or use of other regular medication. Her gynecological examination showed female genitalia with trophism and pubic hair development, both age-appropriate, and no injuries.

Isabel Cristina Esposito Sorpreso, MD, PhD
Associate Professor of the Discipline of Gynecology
Department of Obstetrics and Gynecology, Faculty of Medicine, University of São Paulo (FMUSP)

Mailing Address: Tatiana Dias de Carvalho
Florencio Varela, 1903. Postal Code: B1754JEC, San Justo, Buenos Aires - Argentina
E-mail: carvalho.td1@gmail.com

DOI: https://doi.org/10.36660/ijcs.20200002

Manuscript received January 02, 2020; revised manuscript June 29, 2020; accepted August 15, 2020.

She reported no chronic or infectious gynecological diseases. She denied alcohol or drug abuse, but had a history a smoking. The general physical examination showed good general condition, ruddy, hydrated, afebrile, respiratory rate of 19/min, normal blood pressure, body mass index of 33.33 kg/m². Cardiac, pulmonary, abdominal, and biochemical exams showed no relevant findings.

Cardiac autonomic modulation was assessed through HRV analysis. RR interval recordings were obtained by a validated heart rate receiver,[2] placed on the chest, with the patient at rest for 20 min. HRV analysis was performed as proposed by Godoy et al.,[3] using linear (time and frequency domains) and nonlinear methods.[4] Additionally, geometric indexes, Poincaré and recurrence plots, entropy-based techniques, and Detrended Fluctuations Analysis[5] (DFA) were analyzed (Table 1).

Discussion

This study found signs of reduced parasympathetic and global modulation with an apparent increase in the sympathetic tone and a loss of HR fractal dynamics toward correlated behavior, characterized by low entropy and high determinism in a time series.

Our study subject had been using hormonal therapy (HT) (natural estrogen and second-generation progestogen) since having been diagnosed with amenorrhea. Previous studies[1,6] have evaluated the effect of sex hormones and distinct interventions on cardiac autonomic modulation. It is known that menopausal women present a lower HRV when compared with women who are not in menopause,[6] and that HT[7] and exercise[8] can apparently improve cardiac autonomic modulation. Liu et al.,[9] investigated the role of estrogen in gender-related autonomic differences and found that during the postmenopausal period, the vagal and sympathetic activities were lower and higher, respectively.

Effects of oophorectomy on cardiac autonomic modulation revealed an imbalance in the regulation of the cardiovascular system, with a decrease in cardiac vagal modulation and an increase in sympathetic activity.[10] Since our patient underwent a bilateral oophorectomy procedure, this case report also incorporates important

Table 1 – HRV linear and nonlinear indices of the Swyer Syndrome patient

Linear methods		Nonlinear methods	
Time domain		**Recurrence plot**	
Mean RRi (ms)	722.1		
SDNN (ms)	21.3		
Mean HR (1/min)	83.16		
RMSSD (ms)	9.5	Lmean (beats)	16.37
Geometrics		Lmax (beats)	988
RR tri	6.711	REC (%)	41.30
TINN (ms)	105.0	DET (%)	99.43
SD1 (ms)	6.7	ShanEn	3.668
SD2 (ms)	29.3		
SD1/SD2	0.228		
Frequency domain		**Other**	
LF (ms²)	118	ApEn	1.226
HF (ms²)	19	SampEn	1.227
LF (nu)	86.1	DFA alpha1	1.416
HF (nu)	13.9	DFA alpha2	1.007
LF/HF	6.191	alpha1/alpha2	1.406

RRi: RR interval, SDNN standard deviation normal-to-normal intervals, RMSSD root mean square of successive differences, LF low frequency, HF high frequency, nu: normalized units. RRtri: triangular index, TINN: RRi triangular interpolation, SD1: standard deviation of the instantaneous variability in continuous RRis, SD2: standard deviation of long-term continuous RRi: SD1/SD2: ratio between short and long variations of the intervals. Lmean: Mean line length; Lmax: Max line length; REC: Recurrence rate; DET: Determinism; ShanEn: Shannon Entropy. ApEn: Approximate entropy; SampEn: Sample entropy; DFA: Detrended fluctuation analysis.

endocrine features, which, along with genetic features, were both important to understand the modification of cardiovascular risk.

In linear methods, we found lower parasympathetic indices (RMSSD and HF) than the mean values of previous studies.[1] LF and LF/HF were higher, which could be related to an increase in the sympathetic tone.[4,5] SDNN, which presents global modulation, was lower than the mean values of the same studies, which could be due to reduced parasympathetic activity.[4,5]

As no specific studies about Swyer Syndrome with geometric and nonlinear indexes were found, our results have been compared with those from a menopause study[8] with a similar HT. All of this study's geometric indexes, both parasympathetic (SD1) and global indexes (RRtri, TINN, SD2 and SD1/SD2), were reduced. Regarding nonlinear indices, the present study shows higher values. In the DFA analysis, values close to 1.5 are associated with signs of strongly correlated behavior,[5] while our results pointed to a strongly correlated behavior with possible loss of fractal properties. Autonomic conditions characterized by sympathetic predominance or by the reduction in global modulation often present a correlated behavior and decrease in complexity.[5]

Sample Entropy is used to evaluate the complexity of the physiological time-series signals. Approximate Entropy is applied to quantify the amount of regularity fluctuations upon time-series data and is linked with vagal modulation and HF. Higher values indicate more complex data. Shannon entropy quantifies the degree of complexity of the signal's sample distribution. In physiological conditions, where there is a loss of time series complexity, the recurrence of points in the system increases. Their diagonals, such as Lmean, express the similarity of system behavior in two distinct time sequences.[5] In our patient, in general, nonlinear indices showed a loss of HR fractal dynamic toward correlated behavior, characterized by low entropy and high determinism in the time series. REC and DET values were very similar to linear pattern values, typical of reduced complexity.[11]

Our results were then compared with those from Rismini et al.,[12] who evaluated the sympathovagal balance in transsexuals. Their data demonstrated that male-to-female transsexuals (a supposedly similar genetic condition, XY, with HT) displayed significantly lower sympathetic and parasympathetic activities than did the controls, which could be mediated by the effect of hexogen estrogens, since these subjects do not have other protective factors.

To the best of our knowledge, this is the first study in the literature describing HRV nonlinear indices in Swyer Syndrome. However, this study has some limitations. First, because this is a case report, there are limitations regarding comparisons with previous literature. Secondly, it is possible that the individual's BMI and smoking history could alter the HRV parameters. Nevertheless, our study findings point out possible negative effects of hypoestrogenism, gonadectomy, and aging in subjects with DSD, as well as the importance of HT to improve autonomic regulation during one's lifetime.

Conclusion

HRV analysis in Swyer syndrome showed reduced parasympathetic and global modulation with an apparent increase in sympathetic tone and a loss of HR fractal dynamic toward correlated behavior, characterized by low entropy and high determinism in a time series. Our findings suggest that individuals with Swyer syndrome may have increased cardiovascular risk despite HT.

Author Contributions

Conception and design of the research: VX Pereira, ICE Sorpreso. Acquisition of data: VX Pereira, AR Norbeto. Analysis and interpretation of the data: TD Carvalho, VE Valenti. Statistical analysis: TD Carvalho, VE Valenti. Writing of the manuscript: MA Marinovic Junior e JM Soares Júnior. Critical revision of the manuscript for intellectual content: ICE Sorpreso.

Acknowledgments

We are grateful to the patient, who gave her informed consent for publication.

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 post doctoral submitted by Valdelias Xavier Pereira, from F*aculdade de Medicina da Universidade de São Paulo*.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Faculdade de Medicina da Universidade de São Paulo* (FMUSP) under the protocol number 2.368.076. 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. Goldmeier S, De Angelis K, Rabello Casali K, Vilodre C, Consolim-Colombo F, Belló Klein A et al. Cardiovascular autonomic dysfunction in primary ovarian insufficiency: clinical and experimental evidence. Am J Transl Res. 2013, 6(1):91-101.
2. Gamelin FX, Berthoin S, Bosquet L. Validity of the polar S810 heart rate monitor to measure RR intervals at rest. Med Sci Sports Exerc. 2006; 38(5):887–93.
3. Godoy MF, Takakura IT, Correa PR. Relevância da análise do comportamento dinamico não linear (Teoria do Caos) como elemento prognostico de morbidade e mortalidade em pacientes submetidos a cirurgia de revascularização miocárdica. Arq Cienc Saude. 2005; 12(4):167–71.
4. Vanderlei LCM, Pastre CM, Hoshi RA, Carvalho TD, Godoy MF. Noções básicas de variabilidade da frequência cardíaca e sua aplicabilidade clínica. Braz J cardiovasc Surg. 2009; 24: 205–17.
5. Huikuri HV, Makikallio TH, Perkiomaki J. Measurement of heart rate variability by methods based on nonlinear dynamics. J Electrocardiol. 2003; 36:95–9.
6. Jurca R, Church TS, Morss GM, Jordan AN, Earnest CP. Eight weeks of moderate-intensity exercise training increases heart rate variability in sedentary postmenopausal women. Am Heart J. 2004; 147:e21.
7. Yildirir A, Kabakci G, Yarali H, Aybar F, Akgul E, Bukulmez O, et al. Effects of hormone replacement therapy on heart rate variability in postmenopausal women. Ann NoninvasElectrocardiol. 2001; 6(4):280–4.
8. Rezende Barbosa MPDC, Vanderlei LCM, Neves LM, Takahashi C, Torquato PRDS, Fortaleza ACS, et al. Impact of functional training on geometric indices and fractal correlation property of heart rate variability in postmenopausal women. Ann Noninvas Electrocardiol. 2018; 23(1): 1-9.
9. Liu CC, Kuo TB, Yang CC. Effects of estrogen on genderrelated autonomic differences in humans. Am J Physiol Heart Circ Physiol. 2003; 285(5):H2188-93.
10. Mercuro G, Podda A, Pitzalis L, Zoncu S, Mascia M, Melis GB, Rosano GM. Evidence of a role of endogenous estrogen in the modulation of autonomic nervous system. Am J Cardiol. 2000; 85(6):787–9.
11. Takakura IT, Hoshi RA, Santos MA, Pivatelli FC, Nóbrega JH, Guedes DL, et al. Recurrence Plots: a New Tool for Quantification of Cardiac Autonomic Nervous System Recovery after Transplant. Braz J Cardiovasc Surg 2017;32(4):245-52.
12. Resmini E, Casu M, Patrone V, Rebora A, Murialdo G, Minuto F, et al. Sympathovagal imbalance in transsexual subjects. J Endocrinol Invest. 2008: 31(11):1014-9.

Int J Cardiovasc Sci. 2021; 34(4):490-493

CASE REPORT

Catheter Ablation in Neonate with Heart Failure Due to Incessant Atrioventricular Reentrant Tachycardia

Sissy Lara de Melo, José Nilo de Carvalho Neto, Nathalia Maria Segovia Monge, Italo Bruno dos Santos Sousa, Cristiano Faria Pisani, Mauricio Scanavacca

Universidade de São Paulo - Instituto do Coração, São Paulo, SP – Brazil

Abstract

The atrioventricular (AV) reentrant tachycardia (AVRT) is the most common cause of supraventricular tachycardia (SVT) in the young pediatric population. Some newborns might present with congestive heart failure and require interventional treatment. Catheter ablation in small infants (<6 months and <5 kg) is still poorly performed and controversial due to high complications rate in this group of patients.[1] We report a case of a 28 days old infant (3,5 kg) with a drug-refractory left accessory pathway mediated tachycardia and severe hemodynamic compromise, who underwent catheter ablation. Radiofrequency ablation should be part of the therapeutic arsenal in a context of drug-resistant supraventricular tachycardia with hemodynamic compromise, despite the greater risks of complications in this special population.

Case Report

A female neonate, 13 days old, diagnosed with fetal tachycardia, without registries of tachyarrhythmias after birth and no 12-lead ECG record at delivery, was admitted to the emergency department with incessant supraventricular tachycardia, with a heart rate of 250 beats per minute (bpm) (Figure 1).

At the admission in the intensive care unit, adenosine (0.05 mg/kg) was unsuccessfully administered twice. So, electrical cardioversion was performed (0.5J/kg + 1J/kg), with immediate interruption of the arrhythmia, however with prompt recurrence. During sinus rhythm, it was possible to identify ventricular pre-excitation. Echocardiogram showed a left ventricular ejection fraction (LVEF) of 46%.

Due to hemodynamic instability, orotracheal intubation was performed and dopamine started. Loading dose of amiodarone (5mg/kg) was administered in 40 minutes, followed by a maintenance infusion of 10mg/kg daily. In the following days, the patient evolved with acute kidney failure and hydroelectrolytic disturbance. In this context, the newborn developed severe bradycardia requiring the interruption of the amiodarone infusion and peritoneal dialysis. Thereafter, epinephrine and dobutamine were administered.

Amiodarone was restarted after the correction of the hydroelectrolytic disorders, at a dose of 5 mg/kg/day, with dose progression over the next days, reaching up to 30 mg/kg/day. It was not possible to prescribe other available antiarrhythmic drugs due to the ventricular dysfunction, and to the need of vasoactive drugs. Despite that, the 28-day old infant evolved with incessant AV tachycardia, being then decided to attempt RF ablation.

The electrophysiological study was performed after 8h of fasting and under general anesthesia. A single standard 5 French, 4-millimetre tip deflectable quadripolar catheter (5 FR RF – Medtronic Marinr steerable catheter) was

Keywords

Newborn; Supraventricular Tachycardia; Heart Failure; Catheter ablation.

Sissy Lara de Melo, MD, PhD
Assistant Physician of the Arrhythmia Group
Incor - Instituto do Coração, Hospital das Clínicas, FMUSP

Mailing Address: Sissy Lara de Melo
Universidade de São Paulo - Instituto do Coração - Arritmia
Av. Dr. Enéas de Carvalho Aguiar, 44. Postal Code: 05403-000, São Paulo, SP – Brazil.
Email: sissy.lara@incor.usp.br

DOI: https://doi.org/10.36660/ijcs.20200015

Manuscript received on January 31, 2020; reviewed on June 17, 2020; accepted on January 03, 2021.

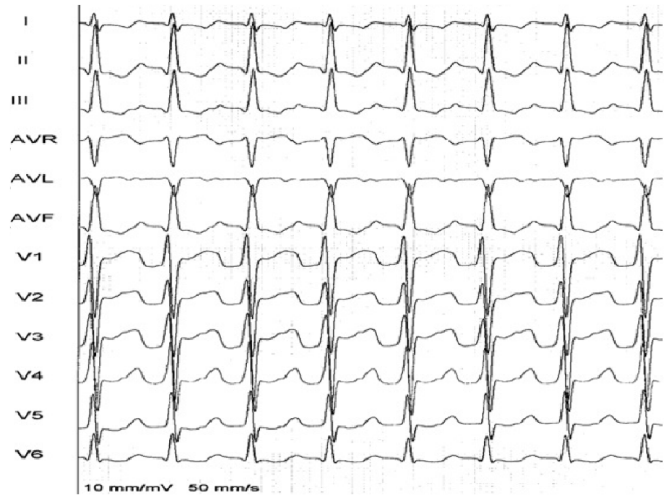


Figure 1 – Electrocardiogram of the neonate showing supra-ventricular tachycardia at a heart rate of 250bpm.

introduced through the left femoral vein for mapping and ablation purposes. Tachycardia was interrupted during programmed stimulation and revealed a left posterior accessory-pathway pre-excitation pattern on the surface EKG (Figure 2). The foramen ovale was used for left atrium access (Figure 3). After administration of 100 units per kilogram of intravenous heparin, RF application was successfully delivered at the targeted site, with immediate conduction block through the accessory pathway (Figure 4). RF application was maintained for one minute with 30W. There were no intra-procedural complications. Right bundle branch block occurred due to mechanical trauma with spontaneous recovery.

During the following hours, the hemodynamic condition improved markedly. The neonate was extubated and inotropic drugs were discontinued after 72h. Patient was discharged 6 days later. No more tachycardias or pre-excitation recurrence have been registered so far. The child remains with no arrhythmias, without pharmacological treatment, 6 years after the procedure. EKG shows sinus rhythm and Echocardiogram has normal ventricular function without segmental lesions.

Discussion

The incidence of tachycardias in the neonatal period is between 1% and 5%.[1,2] AVRT and atrial flutter account for 90% of the fetal and neonatal tachyarrhythmias.[3] In most of these cases pharmacological and eventually electrical cardioversion may be sufficient to obtain satisfactory clinical control. When the arrhythmia recurs, its frequency decreases in the first year of life (90% of patients), and invasive interventions are rarely needed.[4]

It is important to take into account that supraventricular tachycardia may be unrecognized in newborns until heart failure (HF) symptoms emerge; thus, neonates may present a decrease in LV function, or even cardiogenic shock if the correct diagnosis is not given.[5] In this case, despite the diagnosis of fetal tachycardia, an adequate investigation was not performed after birth, and the newborn was discharged without EKG. The SVT diagnosis was only obtained on the 13th day of life, when the child was taken to the emergency room in the context of cardiogenic shock.

To prevent recurrence, antiarrhythmic prophylaxis is recommended during the first year of life. Digoxin or propranolol are generally considered as the initial antiarrhythmic therapy for concealed accessory pathways. In case of first-line drugs failure, class IA (quinidine), class IC (flecainide), or class III (amiodarone or sotalol) drugs can be considered. In manifest accessory pathways, oral propafenone is reasonable for ongoing management in patients without structural or ischemic heart diseases. Oral amiodarone may be considered in patients with AVRT in whom propafenone is ineffective or contraindicated.[6]

The first reports demonstrating safety and efficacy of RF ablation in children were published by the Pediatric

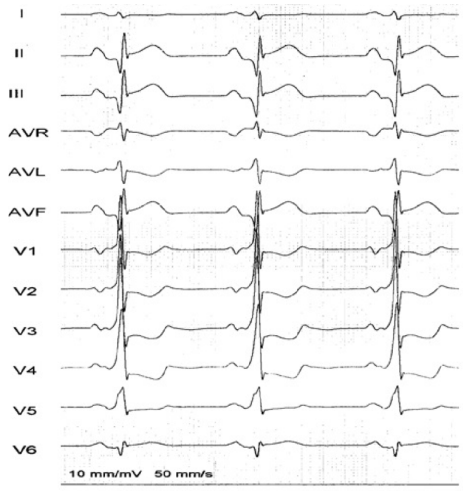


Figure 2 – Post cardioversion ECG in sinus rhythm showing left side ventricular pre-excitation.

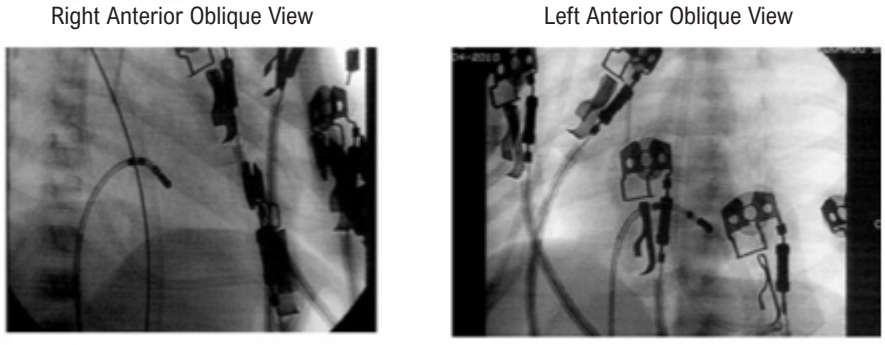


Figure 3 – Right and left oblique fluoroscopic view showing ablation catheter on the mitral annulus accessed through patent foramen ovale.

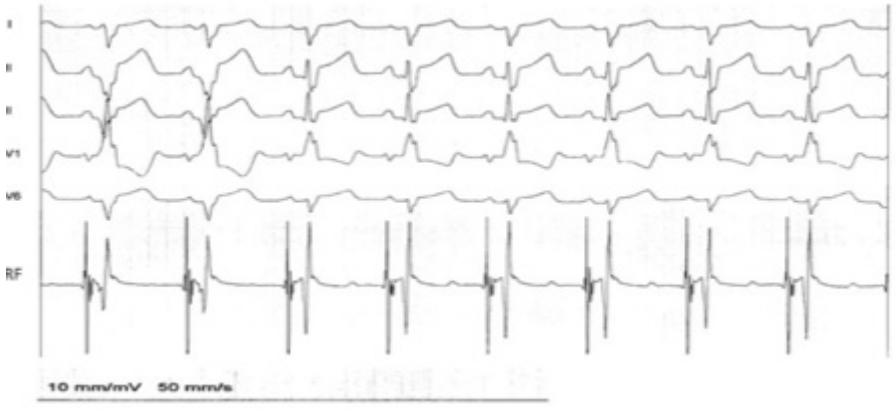


Figure 4 – Surface ECG and endocavitary bipolar signal at the tip of ablation catheter (RF) showing pre-excitation elimination (3rd QRS complex) with maintenance of the mechanical right bundle branch block.

Electrophysiology Society in 1994.[1] In recent periods, publications have shown an evolution in the success rate and a decrease in the number of complications.[7-15]

According to the 2016 HRS SVT guideline, ablation is recommended for documented SVT, recurrent or persistent, when medical therapy is either not effective or is associated with intolerable adverse effects. One must take into account that for very young children, the threshold for ineffectiveness and intolerability should be higher.

Death and major complications are rare, usually related to underlying heart diseases, lower patient weight, greater number of RF applications, and left-sided procedures.[1]

In general, radiofrequency ablation in small infants (less than 5 kg and younger than 6 months of age) should be reserved for life threatening, or refractory arrhythmias, such as the presented case.[1,6]

In conclusion, systematic investigation and a close follow-up is needed in newborns diagnosed with fetal tachycardia. In specific cases, radiofrequency ablation should be considered as the therapeutic approach, having in mind the greater risks of complications in this population.

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.

Author contributions

Conception and design of the research: Melo, SL.. Acquisition of data: Sousa, IBS; Melo, SL. Writing of the manuscript: Melo, SL; Carvalho Neto, JN; Monge, NMS. Critical revision of the manuscript for intellectual content: Scanavacca, MI; Pisani, CF; Melo, SL.

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. Saul JP, Kanter RJ, Abrams D, Asirvatham S, Cohen YB, Blaufox AD, et al. PACES/HRS expert consensus statement on the use of catheter ablation in children and patients with congenital heart disease. Heart Rhythm. 2016 Jun;13(6):e251-89.
2. Ban JE. Neonatal arrhythmias: diagnosis, treatment, and clinical outcome. Korean J Pediatr. 2017 Nov; 60(11):344-52.
3. Jaeggi E, Öhman A. Fetal and Neonatal Arrhythmias. Clin Perinatol. 2016 Mar;43(1):99-112.
4. Cohen MI, Triedman JK, Cannon BC, Davis AM, Drago F, Janousek J, et al. PACES/HRS Expert Consensus Statement on the Management of the Asymptomatic Young Patient with a Wolff-Parkinson-White (WPW, Ventricular Preexcitation) Electrocardiographic Pattern. Heart Rhythm. 2012 Jun;9(6):1006-24.
5. Gopinathannair R, Etheridge SP, Marchlinski FE, Spinale FG, Lakkireddy D, Olshansky B. Arrhythmia-Induced Cardiomyopathies: Mechanisms, Recognition, and Management. J Am Coll Cardiol. 2015 Oct 13;66(15):1714-28.
6. Brugada J, Blom M, Brugada G, Lundqvist C, Deanfield J, Janousek J, et al. Pharmacological and non-pharmacological therapy for arrhythmias in the pediatric population: EHRA and AEPC-Arrhythmia Working Group joint consensus statement. Europace. 2013 Sep;15(9):1337-82
7. Sahin GT, Ozturk E , Kasar T, Guzeltas A, Ergul Y. Sustained tachyarrhythmia in children younger than 1 year of age: Six year single-center experience. Pediatr Int. 2018 Feb;60(2):115-121.
8. AN HS, Choi EY, Kwon BS, Kim GB, Bae EJ, Noh C, et al. Radiofrequency Catheter Ablation for Supraventricular Tachycardia: A Comparison Study of Children Aged 0–4 and 5–9 Years. Pacing Clin Electrophysiol. 2013 Dec;36(12):1488-94.
9. Backhoff D, Klehs S, Muller MJ, Schneider H, Kriebel T, Paul T, et al. Radiofrequency Catheter Ablation of Accessory Atrioventricular Pathways in Infants and Toddlers ≤ 15 kg. Pediatr Cardiol. 2016 Jun;37(5):892-8.
10. Svintsova LI, Popov SV, Kovalev IA. Radiofrequency ablation of drug-refractory arrhythmias in small children younger than 1 year of age: single-center experience. Pediatr Cardiol. 2013 Aug; 34(6):1321-9.
11. Akdeniz C, Ergul Y, Kiplapinar N, Tuzcu V. Catheter ablation of drug resistant supraventricular tachycardia in neonates and infants. Cardiol J. 2013; 20(3):241-6.
12. Turner CJ, Lau KC, Sholler GF. Outcomes of interventional electrophysiology in children under 2 years of age. Cardiol Young. 2012 Oct; 22(5):499-506.
13. Jiang HE, Li XM, Li YH, Zhang Y, Liu HJ. Efficacy and Safety of Radiofrequency Catheter Ablation of Tachyarrhythmias in 123 Children Under 3 Years of Age. Pacing Clin Electrophysiol. 2016 Aug; 39(8):792-6.
14. Femenía F, Sarquella-Brugada G, Brugada J. Single-catheter radiofrequency ablation of a permanent junctional reciprocating tachycardia in a premature neonate. Cardiol Young. 2012 Oct;22(5):606-9.
15. Karmegeraj B, Namdeo S, Sudhakar A, Krishnan V, Kunjukutty R, Vaidyanathan B. Clinical presentation, management, and postnatal outcomes of fetal tachyarrhythmias: A 10-year single-center experience. Ann Pediatr Card 2018;11(1):34-9.

Int J Cardiovasc Sci. 2021; 34(4):494-497

CASE REPORT

Beyond Atherothrombotic Disease in Acute Coronary Syndrome

Mayra Alejandra Mora,[1] Manuela Molano-Perez,[2] Cristian Orlando Becerra-Gonzalez,[3] Kenny Buitrago-Toro,[1,3] Silvana Jimenez-Salazar,[1] Carlos Ortiz[4]

Universidad Surcolombiana Facultad de Salud,[1] Neiva, Huila - Colômbia
Universidad del Rosario,[2] Bogotá - Colômbia
Universidad Tecnologica de Pereira Facultad de Ciencias de la Salud,[3] Pereira, Risaralda - Colômbia
Fundacion Cardioinfantil - Instituto de Cardiologia,[4] Bogotá, Cundinamarca - Colômbia

Abstract

Half of the global population over 20 years of age will be affected by cardiovascular disease. Cardiovascular events in young people is challenging. Spontaneous coronary artery dissection is a non-traumatic and non-iatrogenic separation of the coronary arterial wall and is an uncommon and underdiagnosed cause of acute myocardial infarction predominately found in young women. Medical management has been more widely accepted, with percutaneous and surgery treatment reserved for precise indications. Optimal control of individual risk factors is essential in order to avoid recurrences.

Introduction

Total cardiovascular disease (coronary heart disease, heart failure, cerebrovascular disease, and systemic arterial hypertension) globally affects up to 48% of all adults over 20 years of age, a trend that is increasing in prevalence and mortality, especially in countries of low resources, characterized by a high prevalence of comorbidities.[1]

The incidence of acute myocardial infarction has remained stable over the years, despite international strategies that aim to control risk factors. Two-hundred-thirty cases per 100,000 are reported, with a higher impact in men, African-Americans, and those over 65 years of age.[2]

Keywords

Cardiovascular Diseases/complications; Coronary Thrombosis; Dissection; Young Adult; Pregnancy/complications; Acute Coronary Syndrome; Percutaneous Coronary Intervention.

Coronary disease in adults younger than 45 years of age is always challenging. Their incidence is 0.5 – 2.4 cases per 1,000 people per year and although they sometimes present classical risk factors, there are other associated conditions that must be taken into account, such as metabolic syndrome, familiar hypercholesterolemia, hypercoagulability, toxic substances (cocaine and cannabinoids), autoimmune diseases, or abnormal variants of the coronary arteries. In women, gender-specific risk factors, such as oral contraceptives, hypertensive disorders associated with pregnancy, polycystic ovarian syndrome, and menopausal-linked hypoestrogenism, increase the incidence of new events.[3-5]

This study reports on a case of a 44-year-old female patient with a history of a hypertensive disorder associated with pregnancy. She required temporary antihypertensive treatment, which was subsequently discontinued. Years later, she received medical care due to chest pain, documenting a coronary dissection of the marginal obtuse. Medical treatment was established with good follow-up evolution.

Case report

The patient was a 44-year-old white woman, with a history of preeclampsia 10 years ago, after which antihypertensive treatment was recommended for 6 months, with gradual suspension of medication during

Manuela Molano, MD
Universidad del Rosario
Residente Anestesiología y Reanimación,
Fundación de Ciencias de la Salud
Bogotá - Colombia

Mailing Address: Kenny Buitrago-Toro
Internal Medicine Department, Hospital Universitario Hernando Moncaleano Perdomo, Calle 9 No. 15-25. Postal Code: 410010, Neiva, Huila - Colombia
E-mail: kenny9012@hotmail.com

DOI: https://doi.org/10.36660/ijcs.20200052

Manuscript received March 23, 2020; revised manuscript June 07, 2020; accepted August 29, 2020.

outpatient follow-up. She was admitted to the emergency room, reporting 48 hours of a non-irradiated oppressive chest pain, whcih intensified with effort and partially decreased at rest, associated with decreased functional class NYHA I to NYHA III. The patient was previously asymptomatic. The physical examination documented high blood pressure 170/90 mmHg, with no other relevant data. The electrocardiogram revealed a repolarization disorder in the upper lateral leads (Figure 1), with positive myocardial injury biomarkers (troponin I). Coronary arteriography identified a diffuse arterial narrowing, bordered by normal segments, proximal and distal to the lesion, suggestive of a type 2A spontaneous dissection of the first obtuse marginal artery, with no evidence of atherothrombotic disease.

The thoracic echocardiogram revealed a left ventricle with segmental contractility disorders and mild systolic function compromise of 49%, measured by Simpson. Likewise, a type I diastolic dysfunction was identified due to an alteration in relaxation.

Conservative management under antiplatelet therapy in monotherapy and a beta block was applied with satisfactory clinical evolution. At the six-month follow-up appointment, the patient had completely recovered her functional status, with improvement in left ventricular function and complete resolution of segmental contractility defect.

Discussion

Spontaneous coronary artery dissection (SCAD) is defined as the separation of the middle and the intima of a coronary epicardial artery not associated with atherosclerosis, thromboembolism, trauma, or iatrogenesis. It is an uncommon and underdiagnosed cause of acute coronary syndrome (ACS).[5]

Historically, the first report dates from 1931 by Pretty, who identified this condition during an autopsy of a 42-year-old woman who suffered an apparent sudden death.[6] Its peak incidence is the fourth and fifth decade of life, with a predilection for the female gender in a 4:1 ratio, especially associated, although not exclusive, to the third trimester of pregnancy and postpartum.[6, 7]

Conventional cardiovascular risk factors in this group of patients are uncommon, although the presence of hypertension (30.1%), dyslipidemia (20.3%), and smoking (11.6%) have been reported. Properly for dissecting events, a high prevalence of fibromuscular dysplasia, connective diseases, autoimmune diseases, and stress situations has been reported.[7-9]

SCAD is the cause of 1-4% of all cases of ACS, the vast majority of which appear in women without pregnancy-related conditions. However, when analyzed in pregnant women, SCAD can reach up to 43%, one of the main causes of coronary events in this population.[6,10]

The pathophysiological process is unclear, but a disruption of the vessel through an intimal tear that allows the creation of a false light and subsequent dissection or a hemorrhagic phenomenon of the vasa vasorum that dissects the vessel are considered.[11]

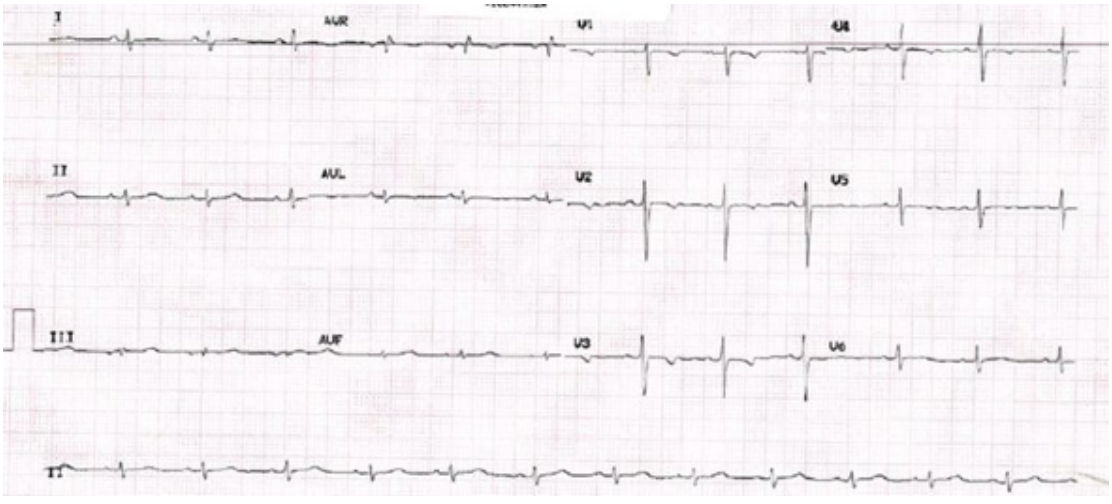


Figure 1 – EKG: sinus rhythm, repolarization disorder in the upper lateral lead

The SCAD properly related to pregnancy can occur during the third trimester, delivery, and early or late postpartum. It is considered that estrogenic and progestogen influx could weaken the arterial walls by altering the content of elastic fibers and mucopolysaccharides, and by decreasing collagen synthesis.[7,12]

The clinical presentation does not vary from that of the ACS due to other causes, although the symptoms may be atypical. The Gold standard for diagnosis is coronary angiography. Intravascular ultrasound, optical coherence tomography, cardiac magnetic resonance, and coronary angiography by computed tomography are also considered highly sensitive and specific.[5,6,13]

Medical conservative management is preferred in hemodynamically stable patients since the affected artery heals spontaneously. Invasive procedures may precipitate, or extend the dissection and even a rupture. Interventional management is indicated for those patients with left main trunk involvement or proximal dissections of more than two vessels associated with hemodynamic instability or refractory angina. Thrombolytic therapy should be avoided.[7-9]

Medical treatment is based on dual anti-aggregation (monotherapy has been reported in low risk patients) for a minimum of 6 months, with a beta blocker (especially if there is left ventricular dysfunction or arrhythmia control) and a strict control of comorbidities. Severe acute stressful situations should be avoided, and Valsalva maneuver activities should be performed. Statins, since there is no atherosclerotic disease, are not recommended[7,10]

Prognosis is usually good. Intrahospital major adverse events were documented in 8.8%, rising to 22% in peripartum. The majority of patients achieve vessel remodeling and spontaneous healing on day 30 in follow-up angiographies, and recurrence is around 10%.[10-13]

In patients who report fibromuscular dysplasia, especially at the renal level with associated renal ischemic disease, stent angioplasty, or renal revascularization, should be considered in order to avoid acute hypertensive crises mediated by renal hypoperfusion.[14]

Conclusion

Coronary dissection is a cause to bear in mind in young women patients with acute coronary syndrome, with or without ST segment elevation, with no associated cardiovascular risk factors. The diagnosis is based on arteriography and is part of the spectrum in cases of MINOCA (myocardial infarction with healthy coronaries). Medical management is essential and actively seeks the underlying cause to prevent recurrences.

Author contributions

Conception and design of the research: Mora MA, Molano-Perez M, Becerra-Gonzalez CO, Buitrago-Toro K, Jimenez-Salazar S, Ortiz C. Acquisition of data: Mora MA, Molano-Perez M, Becerra-Gonzalez CO, Buitrago-Toro K, Jimenez-Salazar S, Ortiz C. Analysis and interpretation of the data: Mora MA, Molano-Perez M, Becerra-Gonzalez CO, Buitrago-Toro K, Jimenez-Salazar S, Ortiz C. Statistical analysis: Mora MA, Molano-Perez M, Becerra-Gonzalez CO, Buitrago-Toro K, Jimenez-Salazar S, Ortiz C. Writing of the manuscript: Mora MA, Molano-Perez M, Becerra-Gonzalez CO, Buitrago-Toro K, Jimenez-Salazar S, Ortiz C. Critical revision of the manuscript for intellectual content: Mora MA, Molano-Perez M, Becerra-Gonzalez CO, Buitrago-Toro K, Jimenez-Salazar S, Ortiz 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 article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Benjamin EJ, Muntner P, Bittencourt MS. Heart disease and stroke statistics-2019 update: a report from the American Heart Association. Circulation. 2019;139(10):e56-e528.
2. Sanchis-Gomar F, Perez-Quilis C, Leischik R, Lucia A. Epidemiology of coronary heart disease and acute coronary syndrome. Ann Transl Med.2016;4(13):256.
3. Andersson C, Vasan RS. Epidemiology of cardiovascular disease in young individuals. Nat Rev Cardiol. 2018;15(4):230-40..
4. Mehta PK, Wei J, Wenger NK. Ischemic heart disease in women: a focus on risk factors. Trends Cardiovasc Med. 2015;25(2):140-51.
5. Filali T, Lahidheb D, Gommidh M, Jdaida B, Hajlaoui N, Fehri W, et al. Spontaneous multivessel coronary artery dissection associated with cannabis use. Journal of cardiology cases. 2013;7(1):e4-e7.
6. Pretty HC. Dissecting aneurysm of coronary artery in a woman aged 42: rupture. Brit Med J. 1931;1:667.
7. Hayes SN, Kim ES, Saw J, Adlam D, Arslanian-Engoren C, Economy KE, et al. Spontaneous coronary artery dissection: current state of the science: a scientific statement from the American Heart Association. Circulation. 2018;137(19):e523-e57.
8. Almaddah NK, Morsy MS, Dishmon D, Khouzam RN. Spontaneous coronary artery dissection: An often unrecognized cause of acute coronary syndrome. Clev Clin J Med. 2019;86(4):252-6.
9. Muñoz C, Perelli J, Robert S, Lindefjeld D, Zalaquett R. Disección coronaria espontánea: comunicación de 2 casos tratados quirúrgicamente. Rev Med Chile. 2016;144(2):257-61.
10. Gilhofer TS, Saw J. Spontaneous coronary artery dissection: a review of complications and management strategies. Expert review of cardiovascular therapy. Curr Opin Cardiol.2019;17(4):275-91.
11. Saw J, Starovoytov A, Humphries K, Sheth T, So D, Minhas K, et al. Canadian spontaneous coronary artery dissection cohort study: in-hospital and 30-day outcomes. Eur Heart J. 2019;40(15):1188-97.
12. Hassan S, Prakash R, Starovoytov A, Saw J. Natural history of spontaneous coronary artery dissection with spontaneous angiographic healing. JACC: Cardiovascular Interventions. 2019;12(6):518-27.
13. Saw J, Humphries K, Aymong E, Sedlak T, Prakash R, Starovoytov A, et al. Spontaneous coronary artery dissection: clinical outcomes and risk of recurrence. Journal of the American College of Cardiology. 2017;70(9):1148-58.
14. Narula N, Kadian-Dodov D, Olin JW. Fibromuscular dysplasia: contemporary concepts and future directions. Progress in cardiovascular diseases. 2018;60(6):580-5.

SEE IN THE NEXT EDITION

Vol. 34, Nº 5, September and October 2021

Embolic Stroke of Undetermined Source (ESUS) and Stroke in Atrial Fibrillation Patients: not so Different after all?

Valeria Cristina Scavasine, Gustavo da Cunha Ribas, Rebeca Teixeira Costa, Guilherme Henrique Weiler Ceccato, Viviane de Hiroki Flumignan Zétola, Marcos Christiano Lange

Transfusion of Blood Products in the Postoperative of Cardiac Surgery

Antonieta Moraes , Juliana Neves Giordani , Cristiane Tavares Borges , Pauline Eloise Mariani , Laura Maggi da Costa, Leonardo Hennig Bridi , Ari Tadeu Lirio dos Santos , Renato Kalil

Echocardiographic and Ultrasonographic Parameters Associated with Protein-losing Enteropathy in Patients with Fontan Physiology: a Systematic Review with Meta-analysis

Marianna Freitas Mourato, Felipe Alves Mourato, Sandra da Silva Mattos, Juliana Rodrigues Neves

Effects of Low-to-Moderate Doses of Anabolic Steroids on Lipid Profile and Muscle Hypertrophy in Resistance Training Practitioners: A Systematic Review with Meta-Analysis

Mário César Carvalho Tenório, Cláudio Luiz Paz, Flávia Valladares, Marcelo Guimarães Junior, Cloud Kennedy Couto de Sá, Luis Correia

Continuous Aerobic Training and High Intensity Interval Training Increase Exercise Tolerance in Heart Failure Patients: A Retrospective Study

Diego Busin, Alexandre M. Lehnen, Olga S. Tairova, Eduardo P. Comparsi, Daniela Carneiro, Micael Potter, Luís F. Deresz, Pedro Dal Lago, Ramiro B. Nunes

Does Hypertension Knowledge Influence Levels of Physical Activity in Hypertensive Patients From a Southern Brazilian Community?

Rafaella Zulianello dos Santos, Andrea Schaefer Korbes, Eliara Ten Caten Martins, Mateus De Lucca, Leonardo De Lucca, Marlus Karsten, Magnus Benetti

Relationship between Discordance of Low-Density Lipoprotein and Non-High-Density Lipoprotein Cholesterol and Risk Stratification in Acute Myocardial Infarction

Murat Eren, Ozge Kurmus, Turgay Aslan, Kursat Akbuga, Hatice Tolunay

How much do the Patients with Acute Myocardial Infarction Know about Chest Pain, Thrombolytic Therapy, and Other Factors Affecting the Treatment Time in the Emergency Room?

Banu Ozmen, Cenk Conkbayir, Refika Hural, Didem Melis Oztas, Murat Ugurlucan, Barış Okcun, Zerrin Yiğit

QTc, Tp-e Interval and Tp-e/QTc Ratio in Patients with Hypocalcemia-case Control Study

Begum Seyda Avci, Akkan Avci, Arif Aksu, Muge Gulen, Onder Yesiloglu, Hasan Koca, Salim Satar

Cardiovascular Risk Assessment after COVID-19 Infection before Resuming Sports Activities - Practical Flowchart and Meta-Analysis

Luís Puga, Paulo Dinis, Rogério Teixeira, Joana Maria Ribeiro, Hélder Dores, Lino Gonçalves

INTERNATIONAL JOURNAL OF

Cardiovascular SCIENCES