INTERNATIONAL JOURNAL OF

Cardiovascular SCIENCES

Volume 33 – Number 3 | May / June | ISSN 2359-4802 | ISSN online 2359-5647

SBC CLUBE

Um programa de descontos na aquisição de produtos ou serviços em diferentes segmentos.

Conheça os nossos parceiros e comece a usufruir de mais um benefício para os associados.

Acesse já!
cardiol.br/sbc-clube

INTERNATIONAL JOURNAL OF
Cardiovascular
SCIENCES

SUMARY

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 33, Nº 3, May/June 2020
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)

INTERNATIONAL JOURNAL OF
Cardiovascular
SCIENCES

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
<www.onlineijcs.org>

International Journal of Cardiovascular Sciences. 2020; 33(3):199-202

EDITORIAL

COVID-19: A Matter Close to the Heart

Gláucia Maria Moraes de Oliveira[1] and Fausto J. Pinto[2]

Universidade Federal do Rio de Janeiro (UFRJ),[1] Rio de Janeiro, RJ – Brazil
CCUL, Faculdade de Medicina, Universidade de Lisboa,[2] Lisboa - Portugal

The world is facing a new challenge, the novel coronavirus disease 2019 (COVID-19), caused by a betacoronavirus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), phylogenetically identical to the SARS-CoV (severe acute respiratory syndrome coronavirus) and the MERS-CoV (Middle East respiratory syndrome coronavirus) responsible for innumerable deaths in China in 2003 and in the Middle East in 2012, respectively.

On March 11, 2020, the COVID-19 outbreak was characterized as a pandemic by the World Health Organization (WHO).[1] Twenty-three days after that announcement, the cases reported reached 1,056,777 in 182 countries, with 55,781 deaths, most of which occurring in Italy, Spain, France, China and Iran. So far, Brazil has registered 8,195 cases and 335 deaths, while Portugal, 9,886 cases and 246 deaths, figures that have increased steeply since the beginning of the pandemic.[2]

In the face of this exponential increase, mainly in São Paulo and Rio de Janeiro states, multiple safeguarding measures to prevent further spread of the virus, such as school dismissal, event cancellations, reduced bank hours, closure of commerce, except for essential sectors, recommendation for home confinement, and cancellation of public transportation between municipalities and states, have been taken in Brazil, as well as in Portugal and other countries. In the absence of a vaccine and specific therapy, that is actually the only way to restrain viral spread and to prevent the health system overload, which might lead to its collapse, as seen, for example, in Italy and Spain. Person-to-person spread via respiratory droplets disseminated during sneezing, coughing and talking, as well as transmission through contact with contaminated surfaces justifies those measures.[3] The PCR assay for viral RNA detection on respiratory tract samples has been used for the laboratory diagnosis of COVID-19; moreover, wide-scale testing has been adopted to contain the pandemic in other countries.[3] Other types of tests are being developed to assess the population acquired immunity. These tests identify individuals who have developed immunity to the virus, and who can therefore safely return to their usual activities. This will be essential in the second phase of the pandemic.

Analyses by the Imperial College with projections from the COVID-19 cases have estimated, if no action is taken, 7 billion infections and 40 million deaths worldwide in 2020. Furthermore, they have reported that mitigation strategies focused on protection could cut that burden in half, saving 20 million lives, but not without overloading healthcare services, a situation that might be even more severe in lower income settings.[4] This scenario should be avoided at any cost by implementing strict measures that limit the movement of people, as well as social distancing or even isolation. It is worth noting that underreporting, undertesting and delayed confirmatory test results might jeopardize the statistics of any country that does not adopt a strict policy for test performance, as recommended by the WHO.

A study conducted in China with 72,314 patients with COVID-19 (44,672 laboratory-confirmed cases, 16,186 suspected cases, and 10,567 clinically diagnosed cases) has reported mild clinical severity in 81.4% of the sample, severe clinical severity in 13.9%, and critical clinical severity in 4.7%.[3] The most common symptoms were fever, cough, dyspnea, myalgia, fatigue, and diarrhea.[3,5] Other signals and symptoms have been reported, such as sore throat, chest pain, mental confusion, and lethargy.

Keywords

Coronavirus-19 (COVID-19); Severe Acute Respiratory Syndrome; Dyspnea; Risk Factors; Fever; Mortality; Pandemics; Cardiovascular Diseases/complications.

Mailing Address: Gláucia Maria Moraes de Oliveira
Universidade Federal do Rio de Janeiro – R. Prof. Rodolpho P. Rocco, 255 – Prédio do HU 8º 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.20200057

Almost 5% of the infections will have a severe course with acute respiratory distress syndrome, pulmonary bleeding, severe lymphopenia, kidney failure, circulatory shock, and failure of multiple organs.[3,5] The case-fatality rates by age group in Italy (1,625 cases) and China (1,023 cases) differed substantially, 7.2% and 2.3%, respectively, which can be partially explained by the older age distribution in Italy, as well as the presence of more comorbidities among Italians.[6]

One fourth to half of the patients with COVID-19 have chronic conditions, especially cardiovascular (CVD) and cerebrovascular diseases, which increase the risk for a severe course of disease and death. A meta-analysis of six studies conducted in China, including 1,527 patients with COVID-19, has assessed the prevalence of CVD and reported the following proportions: hypertension, 17.1%; heart and cerebrovascular diseases, 16.4%; and diabetes, 9.7%.[7] Another study with 44,672 confirmed cases of COVID-19 in China has shown preexisting comorbidities, such as CVD (10.5%), diabetes (7.3%), and hypertension (6%), which related to a case-fatality rate of 2.3%.[3] Those studies have evidenced the importance of not only chronic diseases but also of age and host immune *status* to COVID-19-related mortality, characterizing a complex, multifactorial and bidirectional model that can comprise the drugs used to treat those pathologies.[8,9]

Acute and chronic cardiovascular complications have been observed and attributed to several mechanisms, such as relative ischemia, systemic inflammation and pathogen-mediated damage, with increased levels of biomarkers, such as troponin I, BNP, and d-dimer.[9-11] Myocardial damage was observed in 7.2% of patients with SARS-CoV-2 pneumonia, shock in 8.7%, and arrhythmia in 16.7%, leading to intensive care admission.[9] A meta-analysis with four studies, including 341 COVID-19 patients, has reported a significantly higher standardized mean difference in cardiac troponin I levels in patients with severe disease as compared to those with milder disease (25.6; 95%CI: 6.8-44.5 ng/L).[10] In a retrospective multicenter cohort study in China, elevated d-dimer levels at admission (> 1μg/mL) have been associated with in-hospital death even after adjustments (OR 18.4; 95% CI: 2.6-128.6 μg/mL).[11]

Venous thromboembolism in COVID-19 has been reported, probably due to vascular inflammation, hypercoagulable states and endothelial dysfunction.[8] Fulminant myocarditis and heart failure have been associated with SARS-CoV-2 infection; moreover, preexisting coronary artery disease has been associated with a possible predisposition to that infection.[12-14] In a case series with 150 patients with COVID-19, 7% of the 68 deaths were attributed to myocarditis with circulatory failure.[12] Other studies have described fulminant myocarditis with high viral load and the post-mortem finding of mononuclear inflammatory infiltrates in the heart tissue.[13,14] New and important knowledge was recently presented in a case report: the lack of any pulmonary manifestation in a patient with myopericarditis and significant left ventricular dysfunction, who tested positive for SARS-CoV-2 and was successfully treated with dobutamine, lopinavir/ritonavir, steroids, chloroquine, and the usual medical therapy for heart failure.[15] In another study, heart failure has been observed in 23.0% of the COVID-19 patients, being associated with non-survivors (51.9% vs. 11.7%); in addition, the contribution of previous ventricular dysfunction to that outcome remains inconclusive.[11]

Murine models and human post-mortem samples have shown that SARS-CoV can regulate the myocardial and pulmonary angiotensin-converting-enzyme 2 (ACE2), mediating myocardial inflammation, pulmonary edema and acute respiratory failure, and might explain the cardiovascular involvement of severely ill patients.[16] However, data available are still insufficient to determine whether these observations readily translate to humans, and no study has evaluated the effects of renin-angiotensin-aldosterone system inhibitors in patients with COVID-19.[17]

Some studies have suggested that ACE inhibitors (ACEI) and angiotensin-receptor blockers (ARB) can up-regulate ACE2, thus increasing susceptibility to the virus; other studies, however, have shown that ACEI / ARB can potentialize the pulmonary protective function of ACE2.[18,19] The Brazilian Society of Cardiology, the European Society of Cardiology and the American College of Cardiology recommend the individualized assessment of the patient, suggesting that the abrupt withdrawal of therapeutic schemes currently being practiced should not be performed, as that might cause clinical instability and adverse health outcomes.

At the current time there is neither a vaccine against nor a specific treatment for COVID-19. Chloroquine blocks the viral infection by increasing the endosomal pH necessary for the virus/cell fusion and has shown an inhibitory effect on SARS-CoV-2 *in vitro*. Ribavirin, lopinavir/ritonavir and remdesivir are antiviral drugs being tested in prospective studies. It is worth noting that the lopinavir/ritonavir

association alters heart conduction, with QT-interval prolongation and advanced atrioventricular block. In addition, those drugs interact with antiplatelet agents, anticoagulants, statins and beta-blockers .[8,20]

When approaching patients with COVID-19, cardiologists should be alert to new clinical manifestations, such as arrhythmias, left ventricular dysfunction and systemic embolism, which might be related to that condition, since there is much that is still unknow about it.

The COVID-19 pandemic came to change, in a previously unimaginable way, the dynamics and functioning of societies worldwide. The challenges are gigantic, mainly concerning the strain they represent to national health systems, which have never been submitted to such a radical stress test. However, this can also be an opportunity to reorganize and strengthen health systems, and, at the same time, to highlight the pivotal role of health professionals in our society. Policymakers should pursue the most effective way to guarantee the sustainability of health systems, while ensuring that healthcare professionals receive just reward and due recognition for their effort and dedication, often ignored in times of Peace.

The world has responded to this scenario of global crisis with unprecedented widespread solidarity. In light of the enormous challenges that lie ahead, we must ensure that this matter remains close to heart.

References

1. World Health Organization. WHO. Director-General's opening remarks at the media briefing on COVID-19 - 11 March 2020. [Internet]. [Cited in 2020 March 21] [Epub ahead print]. Available from: https://www.who.int/dg/speeches/detail/whodirector-general-s-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020 .Lancet Infect Dis. 2020 Feb 19.pii:S1473-3099(20)30120-1.
2. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020 Feb 19. pii: S1473-3099(20)30120-1. [Epub ahead print] [Cited in 2020 March 20]. Available from: https://www.arcgis.com/apps/opsdashboard/index.html#/bda7594740fd40299423467b48e9ecf6.
3. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72314 Cases From the Chinese Center for Disease Control and Prevention. JAMA.2020 Feb 24. [Cited 2020 February 24]. Available from: https://jamanetwork.com/
4. Imperial College - COVID19-Global-Impact- 26-03-2020; Walker PGT, Whittaker C, Watson O, The Global Impact of COVID-19 and Strategies for Mitigation and Suppression. WHO Collaborating Centre for Infectious Disease Modelling, MRC Centre for Global Infectious Disease Analysis, Abdul Latif Jameel Institute for Disease and Emergency Analytics, Imperial College London (2020) .[Cited in 2020 March 20]. Available from: https://www.imperial.ac.uk/media/imperial-college/medicine/sph/ide/gida-fellowships/Imperial-College-COVID19-Global-Impact-26-03-2020.pdf
5. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020; 395(10223):497-506.
6. Onder G, Rezza G, Brusaferro S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. JAMA. 2020 March 23. DOI: 10.1001/jama.2020.4683. [Epub ahead of print]
7. Li B, Yang J, Zhao F, Zhi L, Wang et al, Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clin Res Cardiol. 2020 Mar 11. DOI: 10.1007/s00392-020-01626-9. [Epub ahead of print]
8. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Bondi-Zoccai G, et al. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic, J am Coll Cardiol. 2020 Mar 18. Pii:S0735-1097(20)34637-4 [Epub ahead of print]
9. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA. 2020 Feb 7. DOI:10.1001/jama.2020.1585.[Epub ahead of print]
10. Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): Evidence from a meta-analysis. Prog Cardiovasc Dis. 2020 Mar 10. pii: S0033-0620(20)30055-4. [Epub ahead of print]
11. Zhou F, Yu T, Du R, Fan G, Liu Y, Xiang J, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 28;395(10229):1054-62.
12. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. Intensive Care Med. 2020 Mar 3. DOI: 10.1007/s00134-020-05991-x [Epub ahead of print]
13. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med. 2020 Feb 18. pii:S221-3-2600(20)30076-X [Epub ahead of print]
14. Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J, et al. Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. Sci China Life Sci. 2020; 63(3):364-74.
15. Inciardi RM; Lupi L, Zaccone G, Italia L, Raffo M, Tomasoni D, et al. Cardiac Involvement in a Patient With Coronavirus Disease 2019 (COVID-19) JAMA Cardiol.2020 Mar 27. DOI:10.1001/jamacardio.2020.1096 [Epub ahead of print]
16. Oudit GY, Kassiri Z, Jiang C, Liu PP, Poutanen SM, Penninger JM, et al. SARS coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest. 2009; 39(7):618–25.
17. Vaduganathan M, Vardeny O, Michel T, McMurray JJV, Pfeffer MA, Salomon SD. Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19DOI: March 30, 2020, N Engl J Med.2020 March 30. [Epub ahead of prnt}
18. Zheng YY, Ma YT, Zhang JY, Xie X. COVID-19 and the cardiovascular system. Nat Rev Cardiol. 2020 Mar 5. DOI: 10.1038/s41569-020-0360-5 [Epub ahead of print]

19. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. Drug Dev Res. 2020 Mar 4. DOI: 10.1002/ddr.21656. [Epub ahead of print]

20. Clerkin KJ. Justin A. Fried, MD, Raikhelkar J., Sayer G, Griffin JM, et al. Coronavirus Disease 2019 (COVID-19) and Cardiovascular Disease. DOI: 10.1161/CIRCULATIONAHA.120.046941 [Epub ahead of print]

International Journal of Cardiovascular Sciences. 2020; 33(3):203-205

EDITORIAL

Infodemia, Fake News and Medicine: Science and the Quest for Truth

Claudio Tinoco Mesquita,[1,2] Anderson Oliveira,[3] Flávio Luiz Seixas,[4] Aline Paes[4]

Pós-Graduação em Ciências Cardiovasculares, Ebserh/HUAP, Universidade Federal Fluminense,[1] Niterói, RJ - Brazil
Hospital Pró-Cardíaco,[2] Rio de janeiro, RJ - Brazil
Comissão Nacional de Energia Nuclear,[3] Rio de Janeiro, RJ - Brazil
Instituto de Computação - Universidade Federal Fluminense,[4] Niterói, RJ - Brazil

"Falsehood flies, and the truth comes limping after it."

Jonathan Swift

Besides fighting against the COVID-19 pandemic, there is another critical problem that Medicine and Science need to face in this crucial moment: the spread of inaccurate information online. By the end of March 2020, more than 2100 Iranians were poisoned by the oral ingestion of methanol. Iran, as an Islamic country, has severe restrictions on alcohol, but in this case, patients told that social media messages suggested they could prevent being infected by SARS-CoV-2 drinking alcohol. Almost 900 illicit alcohol poisoned patients were admitted to the Intensive Care Unit (ICU), and 296 died (fatality rate of 13.5%).[1] In the past, news was produced and distributed by a few organizations or private companies, but today, in the Internet and social media age, anyone can broadcast news online. Fake news is better defined as deliberate false information spread via social or conventional media.[2] Fake medical news can mislead in order to damage an organization and/or a person. Another problematic consequence of a fake medical report is to make profits with some specific food, supplement or treatment.

WHO Director–General Tedros Adhanom Ghebreyesus recently said: "We are not just fighting an epidemic; we are fighting an infodemic". Knowing that stressful times like pandemic are associated with an overload of information and misinformation, immediately after COVID-19 was declared a Public Health Emergency of International Concern, a platform to share tailored information with specific target groups was launched WHO Information Network for Epidemics (EPI-WIN).[3] The infodemic, the global epidemic of misinformation, can have severe consequences to healthcare and for the society. Content created on the web has the potential to provide the right information and to change people's behavior positively. Still, it is also capable of generating opinions and social behaviors that may put health in danger.[4]

The first and most consequential misinformation in public health is the misconception that the measles, mumps, rubella (MMR) vaccine causes autism created by a fraudulent article published in Lancet.[5] This misinformation was widely disseminated on social media and, combined with conspiracy theories and other beliefs strength an anti-vaccination movement. As a consequence, in 2020, many countries, including the United Kingdom, Greece, Venezuela, and Brazil, have lost their measles elimination status.[6,7] In cardiology, there are examples of fake news too. Social media disseminated much misinformation about the potential oncogenic effect of antihypertensive drugs driving many patients to stop using some proved beneficial medication. Battistoni et al. demonstrated that there is any support to promote or encourage the banning of antihypertensive drugs because of a possible risk of neoplasms.[8] O'Connor makes a strong argument calling cardiologists to firmly oppose exaggerated therapies, untested entities, unproven vaccines, and nutraceuticals taking the example of heart failure fake news.[9]

Widening the quote of Jonathan Smith, fake news diffuses significantly farther, more quickly, deeper, and

Keywords

Coronavirus; Information Dissemination; Scientific Misconduct/trends; False Representation; Information Science/trends; Disaster Medicine/ethics.

Mailing Address: Claudio Tinoco Mesquita
Universidade Federal Fluminense Faculdade de Medicina - Departamento de Radiologia - Av. Marques do Paraná, 303. Postal Code: 24230-322, Centro, Niterói, RJ – Brazil
E-mail: claudiotinocomesquita@id.uff.br

DOI: https://doi.org/10.36660/ijcs.20200073

more largely than the truth.[10] As robots accelerate the spread of true and false news at the same rate, implying that false news spreads more than the truth because humans, not robots, are more likely to spread it.[10] This is particularly important, as Pennycook et al identified that having had previous contact with information (familiarity) increases the feeling that this information is true. Furthermore, they also demonstrated that repetition amplifies this feeling of "illusory truth".[11] How can we fight against this threat (figure 1)?

A promising approach to that is to rely on computational methods to detect fake news and misinformation. The majority of techniques to tackle this problem are developed in the area of Artificial Intelligence (AI), mainly using Natural Language Processing (NLP) and Machine Learning (ML) methods. To automatically classifying a piece of text as fake news or not, other ML and NLP solutions are also of aid, including features extraction,[12] social context modeling,[13,14] knowledge-based systems,[15] sentiment analysis,[16] among others.

Feature extraction is particularly important to provide useful information to ML methods. They can be gathered either directly from the text or from external sources. Examples of them include 1) title representativeness, 2) quotes of external sources, 3) presence of citations of other organization and studies, 5) use of logical fallacies, 6) emotional tone of the article, 7) inference consistency, e.g., a wrong association and causation or making a fact to generalize into an incorrect conclusion, 8) originality, 9) credibility of citations, 10) number of ads, 11) confidence degree in the authors, 12) number of social calls, and others. The ML algorithms can use some of these features to approximate a classifier model able to distinguish between a fake and a truthful content. The classifier learning process uses a previously annotated data set as a training set, where the examples in this dataset are the articles, and the annotation is if it is fake or not. In some cases, it is necessary to pre-process the data before extracting the features, using, for example, tokenization (divide the text into smaller parts called tokens), lower casing transformation, removal of common words that lack a proper meaning (stop words), sentence segmentation, etc.[12] Besides relying on feature engineering and extraction, recent methods based on Deep Learning take into account the content of the texts directly, in an end-to-end fashion. For example, Fang et al. developed a model to judge the authenticity of news with a precision rate of 95.5% based only on their content by using convolutional neural networks and self multi-head attention mechanism.[17]

Other AI promising approaches consist of analyzing the social network features that hold the possible fake information. This scenario is relevant because it is increasingly common to use non-human accounts or bots to create fake news and spread them into a social network.[15] Thus, analyzing those social networks users' profiles, for example, can provide useful information for fake news detection. Furthermore, post-based features focus on analyzing how people

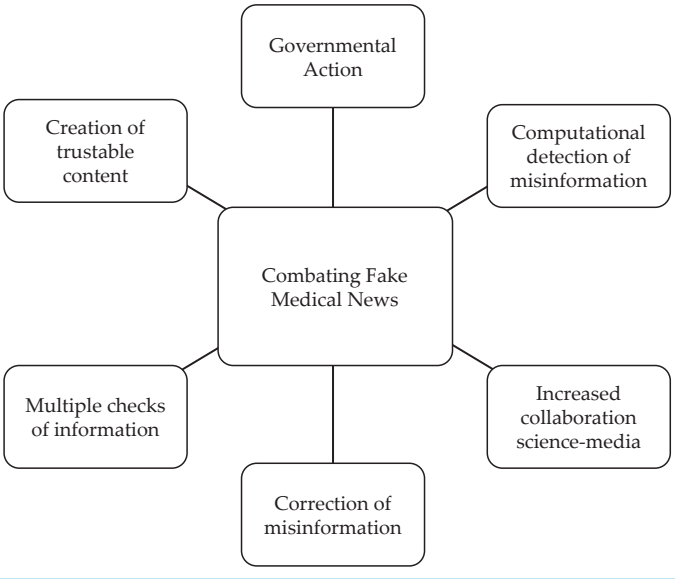

Figure 1 – Proposed strategies for combating fake medical news.

express their opinions towards fake news through social media posts. Users shape different networks on social media in terms of interest, topics, and relations. Network-based features evaluate the network patterns whose user belongs.

One crucial strategy to avoid the dissemination of fake news is providing evidence-based information to the general public by liable organizations and institutions like WHO, OPAS, national health authorities, and academic societies.[3] Linked to the previous action is the creation of health content that is accessible for laypeople, increasing the collaboration of journalists and scientists to minimize errors in communication.[6] Finally, all physicians and healthcare providers should always elicit corrective information when confronting fake news. This strategy is proved to be useful, and the repetition of corrections also appears to be successful for reducing the effect of misinformation.[6] Applying multiple checks with social media information, detecting and avoiding information growth, and recognizing profit-related motivation is vital for managing fake medical information.[2] As in the well-succeeded anti-smoking strategy, the government participation is essential in the fight against fake news. Combating false information must be seen not only as a momentary action, but also as a continuous effort. Thus, creating regulatory support, implementing educational actions and paying special attention to children and young adults are essential.[18]

In summary, we are engaged in a new and never imagined situation as the COVID-19 pandemic is spreading. Fake news can lead to particularly serious health events. All scientists, physicians, healthcare collaborators must work together to fight fake medical misinformation. This fight must not be lost.

References

1. Soltaninejad K. Methanol Mass Poisoning Outbreak: A Consequence of COVID-19 Pandemic and Misleading Messages on Social Media. Int J Occup Environ Med. 2020;11(3):e1–e3.
2. Kanekar AS, Thombre A. Fake medical news: Avoiding pitfalls and perils. Fam Med Community Heal. 2019;7(4):1–4.
3. Zarocostas J. How to fight an infodemic. Lancet. 2020;395(10225):676.
4. Lara-Navarra P, Falciani H, Sánchez-Pérez EA, Ferrer-Sapena A. Information management in healthcare and environment: Towards an automatic system for fake news detection. Int J Environ Res Public Health. 2020;17(3):1-12.
5. Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, et al. Retracted: Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet. 1998;351(9103):637–41.
6. Swire-Thompson B, Lazer D. Public Health and Online Misinformation: Challenges and Recommendations. Annu Rev Public Health. 2020;41(1):433–51.
7. Medeiros EAS. Entendendo o ressurgimento e o controle do sarampo no Brasil. Acta Paul Enferm. 2020 Mar;33:e-EDT20200001.
8. Battistoni A, Tocci G, Presta V, Volpe M. Antihypertensive drugs and the risks of cancer: More fakes than facts. Eur J Prev Cardiol. 2019 Oct;0(00):1–5.
9. O'Connor CM. Heart Failure Fake News: How Do We Distinguish the Truth? JACC Hear Fail. 2019;7(4):363.
10. Vosoughi S, Roy D, Aral S. The spread of true and false news online. Science (80-). 2018 Mar;359(6380):1146–51.
11. Pennycook G, Cannon TD, Rand DG. Prior exposure increases perceived accuracy of fake news. J Exp Psychol Gen. 2018 Dec;147(12):1865-1880.
12. Ahmed H, Traore I, Saad S. Detecting opinion spams and fake news using text classification. Secur Priv. 2018;1(1):e9.
13. Ozbay FA, Alatas B. Fake news detection within online social media using supervised artificial intelligence algorithms. Phys A Stat Mech its Appl. Feb 2020;540:123174.
14. Kapusta J, Obonya J. Improvement of Misleading and Fake News Classification for Flective Languages by Morphological Group Analysis. In: Informatics. Informatics.(Multidisciplinary Digital Publishing Institute); 2020;7(1):4.
15. Shu K, Sliva A, Wang S, Tang J, Liu H. Fake news detection on social media: A data mining perspective. ACM SIGKDD Explor Newsl. 2017;19(1):22–36.
16. Rubin VL, Chen Y, Conroy NJ. Deception detection for news: three types of fakes. Proc Assoc Inf Sci Technol. 2015;52(1):1–4.
17. Fang Y, Gao J, Huang C, Peng H, Wu R. Self Multi-Head Attention-based Convolutional Neural Networks for fake news detection. PLoS One. 2019;14(9):1-13.
18. Tavares SS, Martins M Campos, Faria FR, Cotta R. Combate ao Tabagismo no Brasil: a importância estratégica das ações governamentais. Ciênc. saúde coletiva [Internet]. 2014; 19(2): 539-52.

EDITORIAL

Challenge in the Treatment of Children with Congenital Heart Disease: Reducing Waiting Time for Cardiac Surgery

Ana Flavia Malheiros Torbey and Aurea Grippa

Universidade Federal Fluminense, Niterói, RJ – Brazil

Congenital heart disease is an important cause of mortality in the neonatal period.[1] in Brazil, according to data from DATASUS from the period between 2012 and 2016, congenital heart disease is the third most common malformation in children younger than 28 days, with an estimated incidence of 1.3-1.7% and high mortality rate in this age range. They are also the third main cause of global mortality in the first 30 days of life, the main cause among congenital abnormalities. Therefore, 28,000 new cases per year are expected in Brazil.[2,3]

The outcomes of congenital heart disease can be grouped into spontaneous resolution of minor lesions, such as some interatrial or interventricular communications or persistent arterial duct; conditions that require repair procedures (interventional catheterizations or surgeries); and those cases that only palliative procedures can be performed due to anatomical and physiological features. Thus, approximately 20% of cases do not require surgery and resolve spontaneously, and nearly half of the other 80% (22,400 children) will require cardiac surgery in the first year of life.[4,5]

In the last four decades, advances in surgical and anesthetic techniques, adaptation of neonates to cardiac catheterization, in addition to improvements in post-operative follow-up have changed the natural history of congenital heart disease, as most of the patients did not reach adult life in the past.[3,6] The early diagnosis of critical congenital heart disease, performed during prenatal care by fetal echocardiography, and neonatal screening by pulse oximetry have enabled the planning of appropriate treatment, increase in survival in the neonatal period and consequent improvement in the prognosis.[7]

However, despite changes in the diagnosis and treatment of congenital heart disease, both prognosis and mortality may vary widely among the countries, due to poor access to healthcare services in developing countries, that show higher mortality rates compared with developed countries.[8]

In Brazil, a continental-size country, there is also inequality between its geographic regions, with treatment gaps of nearly 90% in the northern and northeastern regions.[4,5,8] Today, there are 69 centers of the Brazilian Unified Health System (SUS) where pediatric cardiac surgery can be performed, according to data published by the Brazilian Ministry of Health, 2017. However, in 49% of the specialized services, the minimum predicted pediatric surgeries for congenital heart disease is not reached, with an annual average of 17 surgeries per year, which is far lower than the expected 120 surgeries/year per pediatric center.[4]

Therefore, one of the greatest challenges in the management of children with heart diseases is to provide adequate access of these patients to appropriate treatment and follow-up, be it cardiac surgery or interventional catheterization. Jesus et al. report the size of this challenge in the article entitled *Fila de Espera para Tratamento de Pacientes com Cardiopatia Congênita: Retrato de um Centro de Referência Amazônico*.[9] In this report, the mean waiting time for elective hemodynamic procedures was 23.1 ± 18.3 months. Such long waiting time has severe consequences, as it leads to a delay in adequate treatment, worse prognosis, increased number of hospitalizations, and high morbidity and mortality rates. The authors also highlight another issue to be addressed – the poor access of this population to primary health care, for diagnosis of the diseases and referral to treatment, surgical or not.

Keywords

Heart Defects, Congenital/surgery; Public Health; Health Services Accessibility; Public Policy.

Mailing Address: Ana Flavia Torbey
Faculdade de Medicina - Hospital Universitário Antonio Pedro - Rua Marques do Paraná, 303. Postal Code: 24220-900, Niterói, Rio de Janeiro, RJ - Brazil
E-mail: anaflaviamalheiros@gmail.com, aureagrippa@id.uff.br

DOI: https://doi.org/10.36660/ijcs.20190013

Recently, the Brazilian Ministry of Health, with the objective to expand the healthcare provided to children with heart diseases, approved a national action plan for children with congenital heart disease, the *Plano Nacional de Assistência à Criança com Cardiopatia Congênita*, aiming at establishing guidelines and actions that promote the access to diagnosis, treatment and rehabilitation of children and adolescents with congenital heart disease.[10] Investments not only in reducing waiting time for surgical treatment, but also in providing access to appropriate care, since diagnosis in the prenatal period until treatment, could have an impact on morbidity and mortality in this children with congenital heart disease, with direct effects on children mortality rates, mainly in early neonatal period.[11]

Jesus et al.,[9] also draw attention to the fact that most of heart diseases diagnosed in the study population were potentially treatable by cardiac catheterization (65.2%), such as persistent arterial duct, small interatrial communication, coarctation of the aorta and pulmonary valve stenosis. Therefore, to reduce the waiting time for cardiac surgery, the authors suggest the investment in percutaneous treatment, as it requires shorter hospitalization time, thereby promoting higher bed turnover rates in intensive care units and pediatric wards. Also, the authors discuss several strategies to improve health care for this group of patients, such as the development of specialized units and investments in diagnostic methods such as computed tomography angiography and magnetic resonance.[8,9]

Therefore, improvements in health care for heart disease children must be a priority. To this end, a combined effort of public power, health professionals and society is needed.

References

1. Van der Linde D, Konings EEM, Slager MA, Witsenburg M, Helbing WA, Takkenberg JJ, Roos-Hesselink JW. Birth Prevalence of Congenital Heart Disease. J Am Coll Cardiol. 2011;58(21):2241-7.
2. Brasil. Ministério da Saúde. DATASUS.[acwsso em 2019 abr 15]. Disponível em: http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sinasc/cnv/nvuf.def.
3. Bernier PL, Stefanescu A, Samoukovic G and Tchervenkov CI. The challenge of congenital heart disease worldwide: epidemiologic and demographic facts. Sem thorac cardiovasc surg. Pediatr Card Surg Annu. 2010;13(1):26-34.
4. Brasil. Ministério da Saúde. Governo federal lança plano para ampliar atendimento de crianças com cardiopatia congênita. [Acesso em 2019 jan 11]. Disponível em:http://portalarquivos2.saude.gov.br/images/pdf/2017/julho/11/21.06_Cardiopatia%20Congenita%20pediatrica.pdf
5. Pinto Jr VC, Rodrigues LC, Muniz CR. Reflexions about formulation of politics for attention to cardiovascular pediatrics in Brazil. Braz J Cardiovasc Surg. 2009;24(1):73-80.
6. Khairy P, Ionescu-Ittu R, Mackie AS, Abrahamowicz M, Pilote L, Marelli AJ. Changing Mortality in Congenital Heart Disease. J Am Coll Cardiol. 2010; 56(14):1149-57.
7. Kemper AR. Lam WKK, Bocchini JA. The Success of State Newborn Screening Policies for Critical Congenital Heart Disease. JAMA. 2017; 318 (21): 2087-8.
8. Lopes SAVA, Guimarães ICB, Costa SFO, Acosta AX, Sandes KA, Mendes CMC. Mortalidade para Cardiopatias Congênitas e Fatores de Risco Associados em Recém-Nascidos. Um Estudo de Coorte. Arq Bras Cardiol. 2018; 111(5):666-73.
9. Jesus VS, Nascimento AM, Miranda RA, Lima JS, Tyll MAG, Veríssimo AOL. Fila de Espera para Tratamento de Pacientes com Cardiopatia Congênita: Retrato de um Centro de Referência Amazônico. Int J Cardiovasc Sci. 2018;31(4)374-82
10. Brasil. Ministério da Saúde. Portaria 1.727 de 11 de julho de 2017. Aprova o Plano Nacional de Assistência à Criança com Cardiopatia Congênita. [Acesso em 2019 jan 10]. Disponível em: http://bvsms.saude.gov.br/bvs/saudelegis/gm/2017/prt1727_12_07_2017.html.
11. Salim TS, Soares GP, Klein CH, Oliveira GMM. Mortalidade por Doenças e Malformações do Aparelho Circulatório em Crianças no Estado do Rio de Janeiro. Arq Bras Cardiol. 2016; 106(6):464-73

ORIGINAL ARTICLE

Plasma Renin in Women Using and Not Using Combined Oral Contraceptive

Sidney de Souza Oliveira,[1,2,3] Jefferson Petto,[1,4,5] Diego Passos Diogo,[1,6] Alan Carlos Nery dos Santos,[1,6] Marvyn de Santana do Sacramento,[5] Ana Marice Teixeira Ladeia[1]

Escola Bahiana de Medicina e Saúde Pública,[1] Salvador, BA - Brazil
Faculdade de Ciências Empresariais (FACEMP),[2] Santo Antônio de Jesus, BA - Brazil
União Metropolitana de Educação e Cultura (UNIME),[3] Lauro de Freitas, BA - Brazil
Faculdade Adventista da Bahia (FADBA),[4] Cachoeira, BA - Brazil
Centro Universitário Social da Bahia (UNISBA),[5] Salvador, BA - Brazil
Universidade Salvador (UNIFACS),[6] Salvador, BA - Brazil

Abstract

Background: Recent studies show that women on combined oral contraceptives (COC) present abnormal fasting lipid profile, increased postprandial lipemia, plasma C-reactive protein (CRP) and blood pressure (BP) compared to women not on combined oral contraceptives. Plasma renin is one of the factors responsible for abnormal BP.

Objectives: To assess plasma renin levels in women using or not using COC, the correlation between renin and CRP, as well as divergences in lipid profile.

Methods: A cross-sectional study with apparently healthy women aged 20 to 30, eutrophic, irregularly active, and with fasting triglycerides < 150 mg/dL. The sample was stratified into two groups: the No Combined Oral Contraceptive Group (NCOCG), comprised of women who did not use any type of hormone contraceptive, and the Combined Oral Contraceptive Group (COCG) comprised of women on low-dose COC for at least one year. After a 12-hour fast, 5 ml of blood was collected for renin dosing and PCR. Data were analyzed by the t-Test and bidirectional Mann-Whitney Test, both with significance < 0.05.

Results: We evaluated 44 women equally distributed between the groups, age 23 ± 1.2 years, BMI 21.0 ± 3.2 kg/m^2. Median and interquartile deviation of renin in the NCOCG and the COCG were, respectively, 0.5 (0.1-1.0) and 3.0 (2-6) ($p < 0.01$). A positive correlation between PCR and renin ($p < 0.01$ and $r = 0.68$) was found.

Conclusion: The plasma renin levels of women using COC were higher, with a strong correlation with CRP. (Int J Cardiovasc Sci. 2020; 33(3):208-214)

Keywords: Hypertension; Metabolism; Contraceptive, Agents; Risk Factors; Genetics; Dyslipidemias; Diabetes Mellitus; Sedentarism, Women's Health.

Introduction

Several risk factors for cardiovascular disease are shared by women: family history, smoking, dyslipidemia, obesity, diabetes mellitus, arterial hypertension, physical inactivity and, specifically, the use of combined oral contraceptives (COC).[1] Evidence indicates that, in this population, the use of low-dose COC adversely alters the fasting lipid profile,[2] increases postprandial lipemia[3] and increases plasma C-reactive protein levels.[4]

It is also believed that these lipid alterations cause changes in vascular reactivity raising blood pressure levels.[5,6] Researchers in the 1990s showed that women who used COC were more likely to develop high blood pressure compared to women who did not use COC.[7] In a prospective cohort study of approximately 70,000

Mailing Address: Sidney de Souza Oliveira
R. Rio Grande do Sul, 356. Postal Code: 40830-140, Pituba, Salvador, BA - Brazil.
E-mail: sid_ney2011@hotmail.com

DOI: https://doi.org/10.36660/ijcs.20180021

Manuscript received August 15, 2018; revised manuscript April 04, 2019; accepted April 21, 2019.

US nurses with a four-year follow-up (between 1989 and 1993), the relative risk of developing hypertension was 50% higher for current COC users compared to new users and 10% higher compared to long-term users.[8] Translating these into absolute numbers, this increase means 41 cases in every 10,000 women using COC/year. However, at that time, the COCs were not yet of low dose.

More recent studies, which did not aim to assess blood pressure (BP), did not find any statistical difference between the BP of women who used and did not use COC, although systolic and diastolic pressure was higher in women on COC. Despite these results, studies have not yet evaluated the subclinical response of hormonal changes that influence the blood pressure of women taking COC.

Some aspects such as endothelial dysfunction due to reduced nitric oxide intake and changes in the functioning of the renin-angiotensin aldosterone system (RAAS) influence the development of hypertension. RAAS is presented as an endocrine axis in which each component of a cascade is produced by different organs. An arrangement that provides an example of interaction of several organic systems, engaged to maintain hemodynamic stability.[9]

Therefore, the objective of the present study was to test the hypothesis that there is a difference between the plasma renin levels of women who use and do not use COC, as well as to determine their relationship with CRP.

Methods

The present study follows the same data collection protocol from previous studies conducted by our research group.[10] The study is characterized as a comparative cross-sectional observational study in which 44 irregularly active women aged 20 to 30, eutrophic, nulliparous, using COC for at least one year or not using COC were evaluated for at least six months to one year. COCs were considered low dose if they contained 15–30 microgram ethinyl estradiol associated with progestin.

To determine whether the volunteer was irregularly active, the International Short-Form Physical Activity Questionnaire developed by the WHO and the Centers for Disease Control and Prevention (CDC) was used. This questionnaire was used because it has the following advantages: it can be performed in two forms (short and long form), it allows estimating caloric expenditure, presents a more detailed classification, into sedentary, irregularly active, active and very active, besides making it possible to draw comparisons and adjustments to the Brazilian reality.[11]

Exclusion criteria were the presence of diabetes mellitus, dyslipidemia, hepatic dysfunction, glycemia above 99 mg/dL, systemic arterial hypertension, hypo or hyperthyroidism, renal diseases, polycystic ovary syndrome, use of anabolic or dietary supplements, hypo or hyperlipidic diet, history of alcoholism, smoking, use of lipid-lowering drugs, corticoids, diuretics or beta-blockers. For this study, those with total cholesterol > 220 mg/dL, low-density lipoprotein > 160 mg/dL or triglycerides > 150 mg/dL were considered dyslipidemic.

Ethical Criteria

Firstly, the research study was carried out in the Physiotherapy course of Faculdade Social da Bahia. All women who were willing to participate in the study were initially evaluated and those who agreed with the inclusion criteria and did not present any exclusion criteria were included in the study.

All of the research steps, such as the study objectives and the risks and benefits involved in the procedures, were explicitly detailed to the volunteers in a reader-friendly manner. The volunteers signed an informed consent form.

Throughout the study, the human research guidelines of the Declaration of Helsinki and Resolution 466/12 of the National Health Council were observed. This study was submitted and approved by the Research Ethics Committee with CAAE number 79549517.3.0000.5654.

Data Collection Protocol

Participants were divided into two groups. One group using COC (COCG) and one group without COC use (NCOCG). Initially, the volunteers answered a standard questionnaire and were submitted to physical examination. Both were conducted in order to collect general information about the sample characteristics. Physical examination included determination of resting BP, total body mass, height and waist circumference measurements.

To determine BP, the American Heart Association recommendations were followed, using a medium-sized tensiometer for the average adult, duly calibrated by the National Institute of Metrology (INMETRO) and a BD-brand duo-sonic stethoscope.

Height was measured using a professional Sanny stadiometer with 0.1 cm precision. Measurement was

performed with the subjects barefoot and buttocks and shoulders supported in vertical abutment. Total body mass was measured with Filizola digital scales, maximum capacity of 150 kg, measured by INMETRO, with its own certificate specifying a margin of error of ± 100 g.

To measure waist circumference, flexible metallic Starrett tape was used, with measurement definition of 0.1 cm. Abdominal circumference was taken from the lowest curvature located between the ribs and the iliac crest without compressing the tissues. When the slightest curvature could be identified, measurement was taken two centimeters above the umbilical scar. The cut-off points adopted for abdominal circumference were stipulated according to the degree of risk for cardiovascular diseases, namely ≥ 80 cm for women and ≥ 94 cm for men.[12]

BMI was calculated with mass and height measurements, according to the following equation: BMI = mass (kg)/height^2 (cm). The BMI cutoff points adopted were those recommended by the 4th Brazilian Guideline on Dyslipidemia and Prevention of Atherosclerosis, from the Department of Atherosclerosis of the Brazilian Society of Cardiology,[13] that is, low weight (BMI < 18.5); eutrophy (BMI 18.5 – 24.9); overweight (BMI 25 – 29.9) and obesity (BMI ≥ 30).

Five mL of fasting blood sample were collected for the measurement of CRP, total cholesterol and fractions, triglycerides, glycemia and glutamic pyruvic transaminase. The samples were collected by trained professionals in a laboratory environment appropriate for this type of procedure.

PCR was measured by the nephelometry method with plasma serum and precision of 0.1 mg/L. Glycemia, triglycerides, total cholesterol and high-density lipoprotein were obtained by the enzymatic colorimetric method of Trinder. Low-density and very low-density lipoprotein values were obtained by the Friedewald equation. Pyruvic glutamic transaminase was measured by the Reitman-Frankel colorimetric method. Renin was measured by EDTA plasma kinetic radioimmunoassay method.

All volunteers were instructed not to change their diet during the week of collection and to avoid any physical exertion other than usual, as well as not to drink alcohol in the 24 hours prior to the test. NCOCG collection was performed between the fifth and tenth day of the menstrual cycle, considering the lowest hormonal fluctuations, and/or on the 28th day without medication (inactive phase) as recommended by Casazza et al.[14]

Sample size calculation

Sample adequacy calculation was performed with reference to the plasma renin values. A pilot study with six women, three of each group, in which the mean and standard deviation of plasma renin were, respectively, 1.2 ± 0.5 for the NCOCG and 2.6 ± 2.1 for the COCG.

With these data, sample calculation was made in the program GraphPad StatMate 2.0 for Windows, with alpha of 0.05 and beta of 0.8, considering as significant a difference of 0.2 between the groups. The calculation resulted in 21 women in each group. After data collection, a calculation was carried out to determine sample power, which resulted in 0.98.

Statistical analysis

Initially, to determine data distribution, symmetry and kurtosis tests and the Shapiro-Wilk test were conducted. Plasma renin levels did not show normal behavior and were described in median and interquartile range. The other study variables presented normal behavior and were detailed in mean and standard deviation. Abnormal behavior variables were analyzed using the Mann-Whitney test for independent samples. For the variables of usual behavior, unpaired bidirectional Student's t test was used.

Correlation analyses using Spearman's test were conducted between plasma renin and fasting lipid profile variables and plasma renin with PCR. All analyses were performed in the statistical package SPSS (Statistical Package for the Social Sciences) version 13.0, adopting a level of significance of 5%.

Results

Clinical and anthropometric conditions of the sample, 1,970 by 44 women, 22 in each group. Note the homogeneity between the groups, which stands out in the systemic arterial pressure (SBP) (p = 0.02), which is higher in the COCG. A higher level of CRP was also observed in the COCG (< 0.01) (Table 1).

Of the COCs used by the volunteers, 100% contained ethinyl estradiol associated with drospirenone 41% (9), gestodene 27% (6), levonorgestrel 14% (3), chlormadinone acetate 9% (2) and desogrestrel 9% (2). Comparing the fasting lipid variables (Table 2), it can be seen that COCG has a higher triglyceride value (p < 0.01) and total cholesterol (p = 0.02) than NCOCG.

Figure 1 shows the plasma renin value (ng/ml/h) in the groups evaluated. The median and the interquartile deviation of the NCOCG and COCG renin were 0.5 (0.1 – 1.0) and 3.0 (2 – 6), respectively, with significant difference ($p < 0.01$).

Table 1 - Clinical and anthropometric characteristics of the population (n = 44)

Variables	COCG (n = 22)	NCOCG (n = 22)	p value
Age (years)	23 ± 1.3	23 ± 2.0	0.98*
Body mass index (kg/m²)	22 ± 1.4	22 ± 1.0	0.37*
Waist circumference (cm)	73 ± 7.8	70 ± 5.9	0.32*
Systolic blood pressure (mmHg)	119 ± 10.1	107 ± 5.5	0.02*
Diastolic blood pressure (mmHg)	77 ± 6.1	70 ± 10.6	0.18*
C-reactive protein (mg/L)	1.8 (0.5 – 2.2)	0.7 (0.5 – 0.9)	< 0.01#
Glycemia (mg/dL)	82 ± 6.9	83 ± 5.7	0.57*
COC use duration (years)	3.7 ± 2.3		-

*COCG: combined oral contraceptive group; NCOCG: group without combined oral contraceptive. * Two-way t-test for independent samples; # Bidirectional Mann-Whitney test.*

Table 2 - Comparison of fasting lipids (mg/dL) between the groups studied

Variables	COCG (n = 22)	NCOCG (n = 22)	p value
Triglycerides (mg/dL)	88 (72 – 111)	49 (40 – 64)	< 0.01#
Total cholesterol (mg/dL)	207 ± 38.2	183 ± 29.7	0.02*
HDL (mg/dL)	54 ± 13.0	48 ± 11.2	0.10*
LDL (mg/dL)	134 ± 36.4	125 ± 27.2	0.34*

*COCG: combined oral contraceptive group; NCOCG: no combined oral contraceptive group; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL: very low-density lipoprotein. * Two-way t-test for independent samples; # Bidirectional Mann-Whitney test.*

There was also a strong positive correlation between CRP and renin ($p < 0.01$ and $r = 0.68$). The correlation between renin and lipid profile variables showed a moderate positive correlation with LDL ($p = 0.01$; $r = 0.46$). There was not any correlation of renin with the other lipid profile variables ($p > 0.05$).

Discussion

Based on the results of this research study, it is possible to suggest that the use of COC may chronically raise plasma renin values in women who use COC. Although the effects of the sociodemographic and nutritional variables of the study population were not evaluated in greater detail (with the quantity, frequency and types of food consumed), sample homogeneity, elimination of confounding factors in volunteer selection and the power obtained after analysis rule out the possibility of type I statistical error, strengthening the study findings.

According to the 7th Hypertension Guideline of the Brazilian Society of Cardiology,[1] the prevalence of systemic arterial hypertension (SAH) among women using COC is 5%. Since the 1990s, studies indicate that the prevalence of SAH is higher in women taking COC than in those who do not use it.[2,3] In our study, we found that SBP is higher in the group that uses COC, although the values are within normal limits.[1]

The reasons why COC use increases BP are not well established. However, abnormalities may be caused by ethinyl estradiol and progestins in the renin-angiotensin-aldosterone system (RAAS).[4]

Synthetic estrogens increase the hepatic synthesis of the renin substrate by inducing the expression of angiotensinogen mRNA.[5] This increase is also accompanied by enhanced renin activity.[6] This, therefore, increases the production of angiotensin II, which in turn is a potent direct and indirect vasoconstrictor, by inducing the production of vasopressin, when binding to the AT1 receptors in the hypothalamus.[7] In addition, angiotensin II, when converted to angiotensin III, induces the production of aldosterone by the adrenals, which in conjunction with increased production of the antidiuretic hormone (vasopressin) enhance the reabsorption of water through the renal tubules. Both vasoconstriction and increased water retention, induced by this system, favor an increase in systemic BP.[7]

On the other hand, progestins, such as drospirenone, present an anti-mineralocorticoid diuretic effect,

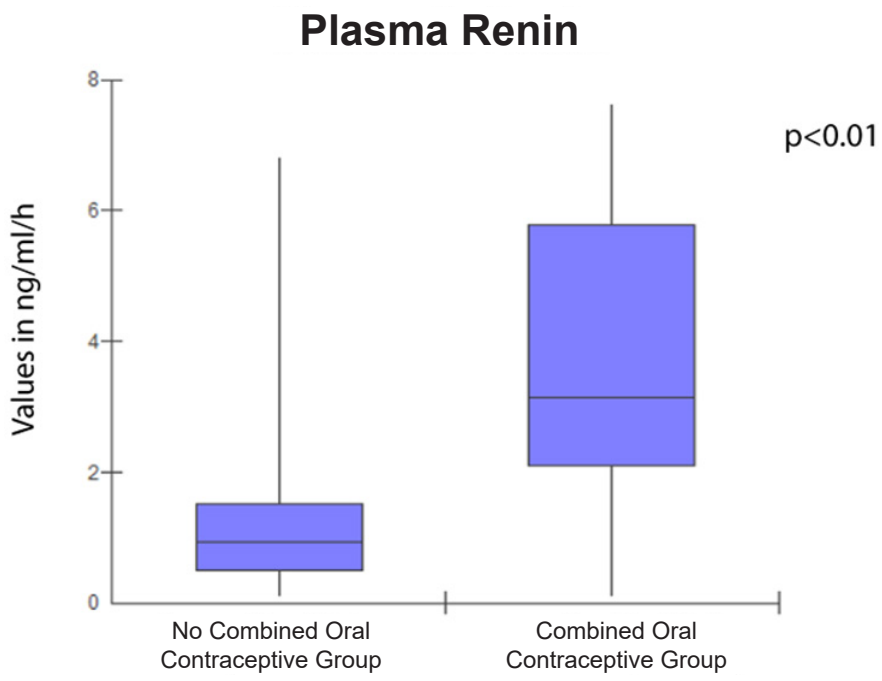

Figure 1 - Median and Interval quartiles of Plasma Renin from the studied groups.

thus reducing BP. In the study by Suthipongse and Taneepanichskul,[8] 120 women were randomized with drospirenone and ethinyl estradiol or levonorgestrel and ethinyl estradiol. The group using drospirenone showed a mean decrease in SBP of 4 mmHg and mean BP lower than the levonorgestrel group. An integrative literature review conducted on articles published between 2012 and 2016, found the same result.[9] In our study, we found that renin values are threefold higher in the COC group. However, because of the sample size, it was not possible to compare the effect of progestin type on plasma renin values.

Increased plasma renin levels increase RAAS activity, which culminates in increased BP. In addition, plasma renin increase is not only associated with increased BP. According to the Framingham study, high plasma renin levels, in addition to increasing RAAS activity, directly contribute to vascular dysfunction, raising the all-cause mortality rate in the general population.[11]

Increased RAAS activity activates other cellular processes, inducing the generation of reactive oxygen species and vascular inflammation that contribute not only to the genesis of hypertension, but also to accelerate damage in the so-called target organs (heart, brain and kidneys).[12]

Studies on inflammation and SAH show a close relationship between infiltration of inflammatory cells and oxidative stress in vascular tissues. RAAS triggers oxidative stress because it stimulates the production of reactive oxygen species such as oxygen superoxide (O2-) and hydrogen peroxide (H2O2). Some studies have contributed to clarifying how RAAS causes elevation in ROS production. Both angiotensin II and aldosterone are capable of inducing the expression of the nicotinamide adenine dinucleotide phosphate oxidase enzyme (NADPH oxidase), a major producer of superoxide anion in vascular tissues.[15]

Nitric oxide, responsible for vasodilation, may have its action altered by the presence of ROS, resulting in increased BP and cellular injury phenomena. This impairment affects the mechanisms of tissue repair and stimulate hyperplasia, hypertrophy and apoptosis, as well as the development of arterial vascular fibrosis.[17] The findings of our study hypothesized that increased renin production in women taking COC promotes increased inflammation and consequently oxidative stress. This

hypothesis is based on the strong positive correlation found between renin and CRP values. We also observed that the CRP values of women using COC were higher than in the non-COC group, corroborating two previous studies produced by our group, which indicates that women using COC have higher subclinical inflammation than women who do not use COC.[11,18]

We can also raise the possibility that high plasma renin levels may re-feed their higher production by stimulating the central nervous system. Increased plasma renin levels by increasing the production of angiotensin II increase sympathetic discharge, since angiotensin II directly stimulates sympathetic activity. Increase in sympathetic activity, in turn, stimulates the beta-adrenergic cells, the glomerular cells of the kidneys, to produce renin.[19]

In summary, increased plasma renin levels appear to be associated with increased subclinical inflammatory activity, which points to the idea that young women with no other risk factors, using COC, are more susceptible to the development of cardiovascular diseases in the medium and long term.

However, in order to assert that COC women are at higher risk of developing cardiovascular diseases, longitudinal studies are necessary to assess cardiovascular dysfunction in this population as primary outcomes. However, it is desirable to evaluate the risks and benefits of prescribing this contraceptive method. Carrying out rigorous clinical follow-up and seeking to evidence potential cardiovascular risk markers, as well as early identifying subclinical inflammation, will be important to prevent the development of cardiovascular diseases in this population in the medium and long term.

Conclusion

Women taking COC have higher serum renin levels and CRP than women who do not use this drug. This points to the possibility that this population is at higher risk of developing systemic arterial hypertension in the long term, which, associated with subclinical inflammation, may increase the risk of cardiovascular diseases.

Limitations

The lack of a detailed nutritional analysis with information on the quantity, type and frequency of carbohydrate consumption, for example, could change some of the evidence, as well as the unchecked sociodemographic aspects.

Author contributions

Conception and design of the research: Oliveira SS, Petto J, Santos ACN. Acquisition of data: Sacramento MS, Santos ACN. Analysis and interpretation of the data: Oliveira SS, Petto J. Statistical analysis: Oliveira SS, Petto J. Análise estatística: Oliveira Writing of the manuscript: Oliveira SS, Petto J, Sacramento MS. Critical revision of the manuscript for intellectual content: Petto J, Ladeia AMT.

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 Sidney de Souza Oliveira, from Escola Bahiana de Medicina e Saúde Pública.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Faculdade Nobre de Feira de Santana* under the protocol number 79549517.3.0000.5654. 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. Malachias MVB, Souza WKSB, Plavnik FL, Rodrigues CIS, Brandão AA, Neves MFT, et al. VII Diretriz Brasileira de Hipertensão Arterial. Arq Bras Cardiol. 2016;107(3 supl.3);1-83.
2. Chasan-Taber L, Willett WC, Manson JE, Spiegelman D, Hunter DJ, Curhan G, et al. Prospective study of oral contraceptives and hypertension among women in the United States. Circulation. 1996;94(3):483-9.

3. Cardoso F, Polonia J, Santos A, Silva-Carvalho J, Ferreira-de-Almeida J. Low-dose oral contraceptives and 24-hour ambulatory blood pressure. Int J Gynaecol Obstet. 1997;59(3):237–43.

4. Abrahão SB, Mion Jr D. Hipertensão arterial e contraceptivos orais. Rev Bras Hipertens. 2000;7(4):392-5.

5. Gordon MS, Chin WW, Shupnik MA. Regulation of angiotensinogen gene expression by estrogen. J Hypertens.1992;10(4):361-6.

6. 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. 2017;19(10):1032–41.

7. Fyhrquist F, Saijonmaa O. Renin-angiotensin system revisited. J Intern Med. 2008;264(3):224-36.

8. Suthipongse W, Taneepanichskul S. An open-label randomized comparative study of oral contraceptives between medications containing 3 mg drospirenone/30 microgethinylestradiol and 150 microglevonogestrel/30 microgethinylestradiol in Thai women. Contraception. 2004;69(1):23–6.

9. Ribeiro CCM, Shimo AKK, Lopes MHBM, Lamas JLT. Effects of different hormonal contraceptives in women's blood pressure values. Rev Bras Enferm. 2018;71(supl. 3):1537-43.

10. Petto J, Pereira LS, Santos ACN, Giesta BA, Melo TA, Ladeia AMT. Subclinical inflammation in women taking oral contraceptives.. Rev Bras Cardiol. 2013;26(6):465-71.

11. Parikh NI, Gona P, Larson MG, Wang TJ, Newton-Cheh C, Levy D, et al. Plasma renin and risk of cardiovascular disease and mortality: the Framingham Heart Study. Eur Heart J. 2007;28(21):2644-52.

12. Fyhrquist F, Saijonmaa O. Renin-angiotensin system revisited. J Intern Med. 2008;264(3):224-36.

13. Wang XL, Rainwater DL, VandeBerg JF, Mitchell BD, Mahaney MC. Genetic contributions to plasma total antioxidant activity. Arterioscler Thromb Vasc Biol. 2001;21(7):1190-5.

14. Casazza GA, Suh SH, Miller BF, Navazio FM, Brooks GA. Effects of oral contraceptives on peak exercise capacity. J Appl Physiol. 2002;93(5):1698-702.

15. Sedeek M, Hebert RL, Ketmedy CR, Burns KD, Touyz RM. Molecular mechanisms of hypertension: role of Nox family NADPH oxidases. Curr Opin Nephrol Hypertens. 2009;18(2):122-7.

16. Taniyama Y, Griendling KK. Reactive oxygen species in the vasculature: molecular and cellular mechanisms. Hypertension. 2003;42(6):1075-81.

17. Kelly DJ, Cox AJ, Gow RM, Zhang Y, Kemp BE, Gilbert RE. Platelet-derived growth factor receptor transactivation mediates the trophic effects of angiotensin II in vivo. Hypertension. 2004;44(2):195-202.

18. Santos ACN, Petto J, Oliveira FTO, Diogo DP, Ladeia AMT. C-Reactive Protein in Oral Contraceptive Users: Related Factors and Cardiovascular Risk. Int J Cardiovasc Sci. 2016;29(4):320-5.

19. Usselman CW, Luchyshyn TA, Gimon TI, Nielson CA, Van Uum SH, Shoemaker JK. Hormone phase dependency of neural responses to chemoreflex-driven sympathoexcitation in young women using hormonal contraceptives. J Appl Physiol. 2013;115(10):1415-22.

International Journal of Cardiovascular Sciences. 2020; 33(3):215-216

EDITORIAL

Oral Contraceptives and Cardiovascular Risk: Adding Clinical Evidence to the Pathophysiology

Daniel Arthur B. Kasal[1,2] and Andrea De Lorenzo[1]

Instituto Nacional de Cardiologia,[1] Rio de Janeiro, RJ – Brazil
Universidade do Estado do Rio de Janeiro,[2] Rio de Janeiro, RJ – Brazil

Women cardiovascular health is an important and often neglected issue. Cardiovascular diseases (CVDs) are the main cause of death in women, in Brazil and worldwide.[1] Oral contraceptives are the main method used for contraception in Brazil.[2] The issue of oral contraceptives and cardiovascular risk has been raised since the first descriptions of this class of pharmaceuticals, in the 1960s. The development of low-dose combined oral contraceptives (COCs) containing ethinyl estradiol and different progestins has reduced, albeit not eliminated, cardiovascular morbidity in women taking these medications.[3] The main side effects associated with COCs are procoagulant effects. Therefore, the use of COCs is associated with increased risk of developing acute myocardial infarction, venous thromboembolism and stroke.[4] In addition, adverse changes in the lipid profile and glucose tolerance have been described.[5] Clearly, ageing and exposure to other risk factors, mainly smoking and obesity, play an important role in the development of adverse outcomes related to COCs. In addition, formulations with different progestins may produce distinct effects on circulation.[6]

Another important side effect associated with COCs is the development of hypertension. A meta-analysis including 24 studies and over 250,000 participants found a significant association between the duration of oral contraceptive use and risk of hypertension.[7] Studies regarding the pathophysiology of this association have revealed a number of different and complementary mechanisms. These include oxidative stress,[8] endothelial dysfunction and the activation of the Renin-Angiotensin-Aldosterone system (RAAS).[9] In this issue, Oliveira et al.,[10] published an interesting clinical observational study, with young volunteers using low-dose COCs for at least one year, compared to women not using the medication. The authors found higher plasma renin levels in women using COC, with a strong correlation with plasma C-reactive protein (CRP). Additionally, although they did not reach the level of hypertension, systolic arterial pressure measurements of COC users were higher than those of non-users. This finding suggests that RAAS activation, if sustained, could eventually shift blood pressure in women using this medication into the hypertension range. The increase of inflammatory pathways, which is associated with RAAS activation, is also shown by the positive correlation with CRP. While the study was restricted to young and healthy participants, and COC use included five different formulations, the results add clinical evidence linking RAAS activation to oral contraceptive use, inflammation and even hypertension development, in a Brazilian sample.

As in all cross-sectional studies, the results cannot establish a cause-effect relationship between COC and CRP elevation or increased blood pressure, but rather suggest an association between them and generate hypotheses. Additionally, it is not possible to exclude that other factors might have influenced the RAAS balance, such as diet, as the authors have already pointed out.

The complexity of the RAAS - with its multiple regulatory pathways - makes its study a challenging task. Nonetheless, the present results of Oliveira et al.[10] highlight the need to thoroughly evaluate cardiovascular risk factors and perform adequate cardiovascular physical examination in patients planning to use COC; and to properly exert regular clinical follow-up of these individuals, aiming at the early diagnosis of adverse effects, such as blood pressure elevation.

Keywords

Oral Contraceptives/adverse effects; Blood Coagulation Factors; Oxidative Stress/drug effects; Hypertension; Woman; Morbidity.

Mailing Address: Daniel Arthur B. Kasal
Av. 28 de Setembro, 77 – 3º andar, sala 329. Postal Code: 20550-900, Rio de Janeiro, RJ - Brazil
E-mail: dabkasal@gmail.com, andlorenzo@hotmail.com

DOI: https://doi.org/10.36660/ijcs.20200078

References

1. Brasil. Ministério da Saúde. Saúde Brasil 2018 uma análise de situação de saúde e das doenças e agravos crônicos: desafios e perspectivas. Brasília; 2019.
2. Farias MR, Leite SN, Tavares NUL,Oliveira MA, Arrais PS, Bertoldi AD, et al. et al. Use and access to oral and injectable contraceptives in Brazil. Rev Saude Publica 2016; 50:14s.
3. Torgrimson BN, Meendering JR, Kaplan PF, Minson CT. Endothelial function across an oral contraceptive cycle in women using levonorgestrel and ethinyl estradiol. Am J Physiol Heart Circ Physiol. 2007; 292(6):H2874-80.
4. Lalude OO. Risk of cardiovascular events with hormonal contraception: insights from the Danish cohort study. Curr Cardiol Rep. 2013;15(7):374.
5. Shufelt CL, Bairey Merz CN. Contraceptive hormone use and cardiovascular disease. J Am Coll Cardiol. 2009;53(3):221-31.
6. Rosendaal FR, Helmerhorst FM, Vandenbroucke JP. Female hormones and thrombosis. Arterioscler Thromb Vasc Biol. 2002;22:201-10.
7. 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.
8. Chen JT, Kotani K. Oral contraceptive therapy increases oxidative stress in pre-menopausal women. Int J Prev Med. 2012;3(12):893-6.
9. Olatunji LA, Seok YM, Igunnu A. Combined oral contraceptive-induced hypertension is accompanied by endothelial dysfunction and upregulated intrarenal angiotensin II type 1 receptor gene expression. Naunyn Schmiedebergs Arch Pharmacol. 2016;389(1):14&-57. 389(1):1147-57.
10. Oliveira SS, Petto J, Diogo DP, Santos AC, Sacramento MS, Ladeia AMT, et al. Plasma Renin in Women Using and Not Using Combined Oral Contraceptive. Int J Cardiovasc Sci. 2020;33(3):208-214.

International Journal of Cardiovascular Sciences. 2020; 33(3):217-224

ORIGINAL ARTICLE

Evaluation of Cardiovascular Risk in Hypertensive Individuals Attending a Primary Health Care Center

Tiago Ricardo Moreira,[1] Luana Vieira Toledo,[1] Érica Toledo Mendonça,[1] Renata Maria Colodette,[2] Luciana Saraiva Silva,[3] Rosângela Minardi Mitre Cotta[1]

Universidade Federal de Viçosa,[1] Viçosa, MG - Brazil
Escola Nacional de Saúde Pública - Sergio Arouca,[2] Rio de Janeiro, RJ - Brazil
Universidade Federal de Uberlândia (UFU),[3] Uberlândia, MG - Brazil

Abstract

Background: Cardiovascular risk (CVR) stratification has traditionally been used as a strategy for the prevention of cardiovascular diseases in asymptomatic people.

Objective: To identify the CVR in hypertensive patients attending a primary health care center, using the Framingham risk score, and to evaluate possible associations and correlations with sociodemographic, clinical and laboratory variables not included in this score. This cross-sectional study was conducted with hypertensive patients treated in a primary health care center in Brazil (n = 166).

Methods: Data collection, administration of questionnaires, anthropometric measurements and laboratory tests were performed from July to August 2013. Multiple linear regression was used in the analysis. A two-tailed p-value < 0.05 was considered significant.

Results: High CVR was independently associated with male sex (B = 8.73; 95%CI: 6.27: 11.19), high serum levels of total cholesterol (B = 0.05; IC95%: 0.02: 0.08), number of drugs used (B = 0.55; 95%Ci: 0.12: 0.98) and a low glomerular filtration rate (GFR) (B = -0.11; 95%CI: -0.18 : -0.03).

Conclusion: The results of this study reinforce the importance of continuous and longitudinal care practices directed to hypertensive patients aiming at early detection of risk factors and appropriate intervention to improve the prognosis of this population. (Int J Cardiovasc Sci. 2020; 33(3):217-224)

Keywords: Cardiovascular Diseases/mortality; Risk Factors; Hypertension; Life Style; Treatment Adherence anf Compliance; Sedentarism; Obesity; Prevention and Control.

Introduction

Arterial hypertension (AH) has been considered one of the main problems of current public health not only because of its high prevalence, but also because of the impact on the quality of life of the population and the health system. According to international data, it is responsible for 45% of cardiac deaths.[1] In Brazil, approximately 36 million adults are affected by the disease, contributing to 50% of deaths from cardiovascular diseases (CVDs).[2]

AH is sometimes considered asymptomatic, which makes the early diagnosis and individuals' adherence to treatment a challenge. However, when untreated, it represents a risk for cardiovascular complications, such as acute myocardial infarction (AMI), stroke and kidney diseases.[3] In light of this, efforts have been directed to the formulation of public policies seeking to identify and intervene on modifiable risk factors.[4]

For an individualized approach of hypertensive patients, the Ministry of Health proposes the use of

Mailing Address: Tiago Moreira
Av. Peter Henry Rolfs, s/n. Postal Code: 36570-000, Campus Universitário, Viçosa, MG – Brazil.
E-mail: tiago.ricardo@ufv.br

DOI: https://doi.org/10.36660/ijcs.20180078

Manuscript received November 06, 2018; revised manuscript June 28, 2019; accepted September 25, 2019.

risk stratification to define the prognosis and clinical approach to hypertension in primary health care (PHC), including the adoption of the Framingham risk score (FRS). The FRS is an algorithm traditionally used as a strategy for preventing cardiovascular diseases in asymptomatic individuals.[3]

To establish a 10-year CVD risk, the FRS considers the following factors: total cholesterol and HDL cholesterol levels, systolic blood pressure, diabetes mellitus, smoking habit and age.[3,5,6] Studies have shown that the score is a potential instrument to help health professionals in the development of more appropriate approaches to hypertensive patients.[5]

In view of the high prevalence of AH and the impact of cardiovascular diseases, studies aiming at identify the cardiovascular risk (CVR) are needed to contribute to the implementation of effective therapeutic measures.[7] The objective of this study was to identify the CVR in hypertensive patients seen at primary health care centers, using the FRS, and to evaluate possible associations and correlations of CVR with other sociodemographic, clinical and laboratory variables not included in this score.

Methods

This is a cross-sectional study conducted with PHC patients with AH in the municipality of Zona da Mata, located in Minas Gerais State, Brazil, in the period from July to August 2013. For sample calculation, a population of 293 patients who participated in educational activities performed in groups, at the primary health care center of the municipality once a month, with an expected frequency of 50% and an error of 5% was considered. A total of 166 patients were selected by random draw.

Data were collected by individual, semi-structured interview, addressing sociodemographic variables and life habits. The International Physical Activity Questionnaire (IPAQ)[8] was applied to identify and quantify physical activity (PA), consisting of questions about the frequency and duration of physical activities at work (moderate and vigorous walking), while commuting, in domestic activities, and in leisure time. PA was measured in minutes per week by multiplying weekly frequency by each event's duration of each. Anthropometric and biochemical assessments were also performed.

Participants were classified as to leisure-time activities as follows:

- sedentary (< 10 min/week, any PA);
- not very active (≥ 10 min to < 150 min/week of walking, moderate PA and/or 10 min to < 60 min/week of vigorous PA and/or 10 min to < 150 min/week of any combination of walking, moderate and vigorous PA);
- physically active (≥ 150 min/week of walking, moderate PA and/or ≥ 60 min/week of vigorous PA and/or ≥ 150 min/week of any combination of walking, moderate and vigorous PA);
- very active (≥ 150 min/week of vigorous PA, or ≥ 60 min/week of vigorous PA plus 150 min/week of any combination of walking and moderate PA).

For dichotomized analyses, participants classified as sedentary and not very active were considered sedentary, and participants classified as physically active and very active were considered active.

Anthropometric assessment was made by weight, height and waist circumference (WC) measurements. Body weight was obtained using an electronic scale, with a capacity of 150 kg and accuracy of 50 grams; and the height was measured using a portable stadiometer, composed of a metallic platform and removable wooden measuring rod containing and a headboard, according to the techniques proposed by Jellife.[9] The BMI (body mass index) was calculated by the ratio between the weight and squared height, and classified according to the WHO criteria for adults,[10] and Lipschitz for elders.[11]

WC measurement was performed using an inextensible tape and measured in centimeters, at the midpoint between the iliac crest and the external face of the last rib. The results obtained were classified according to CVR and metabolic complications according to the cutoff points proposed by the WHO.

Laboratory analyses included: fasting blood glucose, total cholesterol and fractions, triglycerides, serum creatinine, urea, uric acid, and urine albumin (24-hour urine test). Glomerular filtration rate (GFR) was calculated using the CKD-EPI formula.[12]

Participants were explained about the procedure of 24-hour urine collection, in addition to receiving written instructions and containers for urine collection. On the scheduled day, participants attended the accredited laboratory to deliver the urine collected and to have blood samples collected. Participants were instructed to maintain their usual diets on the day before, and blood collection was carried out after a 12-hour overnight fast. Urine volumes less than 500 mL were not included. The collection and analysis of the biological material

was performed in a single accredited laboratory, using commercial kits.

The FRS was applied in all patients to assess the probability of developing a coronary event in 10 years risk of death due to coronary disease. The risk was determined by sex, using the following parameters age, LDL-cholesterol, HDL-cholesterol, smoking, systolic blood pressure, diastolic blood pressure and diabetes.[13]

Analysis

Categorical variables were presented by means of frequency tables (absolute and relative). The Kolmogorov-Smirnov test was used to evaluate the normality of continuous variables. For continuous variables with normal distribution, tables with mean and standard deviation were presented, and, for those with distribution, medians and interquartile intervals were presented.

In the bivariate analysis, the Mann Whitney test for numerical variables with non-normal distribution was used, and the chi-square test was used in the analysis of categorical variables. For correlation between numerical variables, the Spearman correlation was used. Multiple linear regression was performed with CVR as dependent variable, and independent variables that presented a p-value < 0.200 in the bivariate analysis. A two-tailed p-value < 0.05 was considered significant. The necessary assumptions for the application of multiple linear regression were met. The statistical analysis was performed using SPSS for Windows (version 20.0).

The study was approved by the Human Research Ethics Committee of the Federal University of Viçosa, approval number 044/2012. In accordance with Resolution 466/2012 of the National Health Council, which regulates researches involving human beings, the individuals' free and clarified agreement to participate in the study was requested, guaranteeing the confidentiality of the information and anonymity.

Results

Regarding the study sample (n = 166), 130 (78.3%) were female and 36 (21.7%) were male. Mean age of the general population was 62.86 ± 9.3 years, higher in men than in women (64.4 ± 7.36 vs. 61.16 ± 9.68 years, p = 0.034). Median duration of hypertension was nine years with interquartile range (IQR) of 4 to 15 years. Median BMI of the general sample was 28.71 kg/m^2 (IQR: 25.75 - 34.20 kg/m^2). The prevalence of current smokers was 8.4% (n = 14). Sedentary lifestyle was reported by 48 (28.9%) patients. According to the FRS, the median 10-year CVR in the population was 9% (IQR: 7.0 - 15%). Table 1 describes other demographic, clinical and laboratory data of the studied population.

In the bivariate analysis, the CVR was associated with male gender, low educational level, and physical inactivity (Table 2), and exhibited a positive correlation with the number of medications used, and with values of serum urea, glucose, total cholesterol, triglycerides and uric acid. The CVR was negatively correlated with estimated GFR (Table 3).

In stepwise multiple regression model (Table 4), with the risk for a cardiovascular event in 10 years (FRS) as dependent variable, and sex, educational attainment, physical activity, number of medication used, urea, GFR, glucose, total cholesterol, triglycerides and uric acid as independent variables, we observed that sex, serum levels of total cholesterol, GFR and number of medications used by the patients remained independently associated with the FRS ($p < 0.05$). Male gender increased the risk of cardiovascular event by 8.73%. The increase of 1 mg/dL in cholesterol level and the use of medications increased the risk of cardiovascular event by 0.95% and 0.55% respectively. The one-unit increase in mL/min/1.73 m^2 in GFR decreased the risk of a cardiovascular event by 0.11%.

Discussion

In the present study, most of the hypertensive patients evaluated were female, with low educational level, and mean age of 62.86 years. Such findings may be representative of the national population, similar characteristics were found in a population-based study carried out in 2016, showing that a diagnosis of AH was more frequently reported by women (27.5%) than men (23.6%), especially by individuals with up to eight years of study.[14] Low educational attainment and advanced age may increase the prevalence of AH[15] and affect its monitoring and treatment.[16]

The risk factors for coronary artery disease include modifiable lifestyle habits and non-modifiable factors, such as age and sex.[17] The literature indicates that, among the socioeconomic variables, education is the most correlated with the risk factors for cardiovascular diseases, showing an inverse relationship between the degree of schooling and cardiovascular risk.[18] In the

Table 1 - Demographic, clinical and laboratory characteristics of the studied population

Characteristics	General (n = 166)
Age in years (mean ± standard deviation)	62.86 ± 9.30
Sex (F/M) – n (%)	130 (78.3%)/36 (21.7%)
Marital status (with a partner / without a partner) – n (%)	110 (66.3%)/56 (33.7%)
Education (up to 4 years / more than 4 years) – n (%)	140 (84.4%)/16 (15.6%)
Smoker (yes/no) – n (%)	14 (8.4%)/152 (91.6%)
Use of alcohol (yes/no) – n (%)	25 (15.1%)/141 (84.9%)
Physical activity (active/sedentary) – n (%)	118 (71.1%)/48 (28.9%)
Known hypertension length in years – median (IQR)	9.00 (4.00-15.00)
Number of medications – median (IQR)	4.00 (2.00-5.00)
Diabetes (yes/no) – n (%)	35 (21.1%)/131 (78.9%)
Body mass index - median (IQR)	28.71 (25.75-34.20)
Waist circumference - median (IQR)	95.00 (89.00-106.00)
Glomerular filtration rate (mean ± standard deviation)	67.31 ± 13.39
Serum urea - median (IQR)	36.0 (32.0-40.0)
Serum albumin (mean ± standard deviation)	4.01 ± 0.19
Serum glucose - median (IQR)	96.00 (89.00-109.00)
Serum total cholesterol (mean ± standard deviation)	202.59 ± 38.76
Serum HDL-cholesterol - median (IQR)	47.00 (42.00-53.00)
Serum LDL-cholesterol (mean ± standard deviation)	125.81 ± 32.83
Serum VLDL-cholesterol - median (IQR)	26.00 (19.80-34.40)
Serum triglycerides - median (IQR)	130.00 (99.00-172.00)
Serum uric acid (mean ± standard deviation)	5.23 ± 1.31
24h urinary protein - median (IQR)	118.34 (86.40-163.80)
Microalbuminuria - median (IQR)	21.50 (16.00-29.00)
Cardiovascular event risk in % - median (IQR)	9.00 (7.00-15.00)

IQR: Interquartile range; HDL: high-density lipoprotein; LDL: low-density lipoprotein; VLDL very low-density lipoproptein.

Table 2 - Distribution of cardiovascular event risk determined by the Framingham risk score by sociodemographic characteristics and life habits

	Median (IQR)	p-value*
Sex		
Female	8.00 (6.00-13.00)	< 0.001
Male	18.00 (10.00-22.00)	
Marital status		
Without partner	11.00 (7.00-13.00)	0.517
With partner	8.50 (6.00-17.00)	
Education		
Up to 4 years	11.00 (7.00-17.00)	0.004
More than 4 years	7.00 (5.00-9.00)	
Use of alcohol		
Yes	11.00 (6.00-18.00)	0.803
No	9.00 (7.00-15.00)	
Smoker		
Yes	8.50 (7.00-22.00	0.254
No	9.00 (6.00-15.00)	
Physical activity		
Active	8.00 (6.00-15.00)	0.030
Inactive	11.00 (7.00-19.00)	

*IQR: Interquartile range; * U test of Mann-Whitney.*

present study, educational level was not associated with cardiovascular risk. This may be explained by the low degree of schooling of the sample (about 84% of the sample presented less than 4 years of schooling).

Among life habits, although advanced age may decrease the ability to perform some types of physical activity, exercises of mild and moderate intensity, such as hiking, should be encouraged, especially in elderly people.[19] In the present study, the percentage of individuals with a sedentary lifestyle was lower than that reported in other studies.[6,19] One possible explanation is the fact that our study group was composed of a greater percentage of women who performed domestic activites (cleaning, gardening, sweeping), detected by means of the IPAQ. In addition, most of participants were enrolled in health promotion group activities conducted

by the local health system, encouraging the practice of physical activity. In addition, national data show that physical inactivity increases with age, especially among individuals with lower education levels, which contributes to increased CVR in the Brazilian population.[14] In this sense, efforts should be directed towards controlling CVR factors in the population with lower educational attainment.[18,20]

Classification of the CVR is particularly important for establishing an effective and individualized care plan. In this study, the CVR of hypertensive individuals, measured by the FRS, was considered low (median of 9% in 10 years) and associated with male sex, total cholesterol, number of medications used and GFR. In a study on 50 hypertensive individuals treated in a public, multidisciplinary outpatient clinic in Minas Gerais state, Brazil, 74% had low cardiovascular risk.[17] Similar results were found in the Longitudinal Study of Adult Health (ELSA-Brazil) conducted with public employees of higher education institutions in Brazil, where 82.8% of the individuals presented low CVR.[21]

In our study, CVR was higher 8.73% greater in males than females. In the study of the behavior of cardiovascular diseases, the issue of gender cannot be ignored, given the high prevalence of risk factors for these diseases that are associated with sex. In contrast, a study conducted with elderly patients in Goiânia showed that some risk factors for CVDs are more frequent in elderly women, such as dyslipidemia and sedentary lifestyle.[22] In addition, a survey conducted in São Paulo showed that women presented better blood pressure control than men;[23] such results may be related to the behavior of women in relation to their health condition, not only by seeking more health services, but also because they have a greater tendency to follow the proposed treatments.[24,25] In this context, PHC actions must consider individual characteristics, which can facilitate adherence to treatment and, consequently, reduce morbidity and mortality.

Table 3 - Spearman correlation between e cardiovascular event risk determined by the Framingham risk score and the studied variables

	Correlation coefficient	p-value*
Body mass index	-0.025	0.753
Waist circumference	0.088	0.261
Duration of known hypertension (in years)	0.003	0.967
Number of used medications	0.158	0.042
Glomerular filtration rate (GFR)	-0.204	0.008
Serum urea	0.222	0.004
Serum albumin	0.053	0.500
Serum glucose	0.198	0.010
Serum total cholesterol	0.189	0.015
Serum triglycerides	0.170	0.029
Serum uric acid	0.234	0.002
24h urinary protein	0.074	0.342
Microalbuminuria	0.064	0.416

** Spearman Correlation.*

Table 4 - Stepwise multiple linear regression model with cardiovascular event risk determined by the Framingham risk score as dependent variable

	B	Standar error	β	p-value	95%CI	
					Lower	Upper
Sex (male)	8.73	1.25	0.46	< 0.001	6.27	11.19
Total cholesterol	0.05	0.01	0.25	< 0.001	0.02	0.08
GFR	-0.11	0.04	-0.18	0.007	-0.18	-0.03
Number of medications	0.55	0.22	0.17	0.012	0.12	0.98

Note: R2 = 0.19 for model 1 with sex variable; ΔR2 = 0.05 with sex and total cholesterol as independent variables; ΔR2 = 0.04 with sex, total cholesterol and glomerular filtration rate as independent variables; ΔR2 = 0.03 with sex, total cholesterol, glomerular filtration rate and number of medications as independent variables. GFR: glomerular filtration rate.

CVR showed a positive correlation with serum values of total cholesterol. High levels of cholesterol combined with hypertension are associated with an increased risk for coronary disease attributable to CVR fctors,[26] so that educational interventions may be fundamental to reduce cardiovascular morbidity and mortality.[27]

Another important finding of this study was the association between increased use of drugs and increased CVR. A study conducted with patients in northern Minas Gerais found different results, showing a weak correlation between the number of anti-hypertensive drugs and the number of CVR factors in hypertensive patients.[5] In the present study, most hypertensive patients used two or more antihypertensive drugs. This may be explained by an inappropriate use of hypotensive medications, not adjusted to the presence of aggravating factors of cardiovascular risk, and a lack of standardization in the monitoring and management of AH in the PHC.[5]

A study by Egan and colleagues[28] showed that the use of only 1 or 2 antihypertensive, advanced age and a high FRS are independent variables associated with the lack of blood pressure control in hypertensive patients, since individuals with high CVR used other medications, such as aspirin and lipid-lowering drugs. These authors also emphasize the importance of stratifying hypertensive patients using the FRS; once the CVR was identified, patients would benefit from the correct use of medicines, adjusted to their comorbidities, thus contributing to reducing cardiovascular morbidity and mortality, and avoiding the use of unnecessary medications in low-risk patients. Thus, the control of hypertensive patients should not be based solely on blood pressure values, but consist of a comprehensive approach, considering the associated risk factors.[28]

Finally, the increased GFR was associated with reduced cardiovascular risk. According to Go et al.,[29] reduced GFR is associated with the occurrence of cardiovascular events, regardless of the concomitant presence of other classic cardiovascular risk factors. Thus, although the decreased GFR related to age has been considered part of the normal aging process, it represents an independent risk factor for developing cardiovascular disease in elders. [30, 31]

Patients with a GFR between 30 and 45 ml/min/1.73 m², when compared to those with a GFR above 60 ml/min/1.73 m², have 110% increased risk of cardiovascular mortality. Therefore, there is an inversely proportional relationship between GFR and the risk of cardiovascular morbidity, especially cardiovascular mortality.[12,32]

In this sense, actions by interprofessional team at the PHC, must take advantage of the potentialities of the FRS in the classification of CVR, to develop guidelines directed to identify risks, encourage self-care and the shared the responsibility of AH management.[5] In addition, community health workers should be trained for the identification and referral of individuals with CVR factors, contributing to the management of hypertension and its complications. These workers can deal with a more systemized monitoring system and have direct contact with the users of the PHC services.[33] Also, actions of the interprofessional team should be directed to changes in life habits, including the use of technologies in health promotion and prevention of diseases related to AH in hypertensive patients.[34]

This study highlights the important role of regular educational activities aimed at promoting healthier life habits and reducing CVR factors. Nevertheless, although PHC is a potential scenario for managing AH by means of the FRS, studies have revealed that most of hypertensive patients habe not been attended by health teams as advocated by guidelines for the management of chronic diseases,[5,24,35] highlighting the findings of this study to strengthen the appropriate management of these individuals.

The main limitation of this study is related to the study type. Investigations of observational nature do not allow assessing the relationship between cause and effect, despite the association between the studied variables. Another limitation relates to the fact that the study has been performed with a specific sample of hypertensive patients, attending the PHC center of one municipality. Expanding the study to other regions and cities could be useful to analyze the reproducibility of the results.

Conclusion

This survey on CVR factors in hypertensive patients seen in a PHC center determined the health profile of this population, highlighting the need for specific interventions by the interprofessional team. The CVR was associated with male sex and had a positive correlation with the number of medications used and elevated serum values of total cholesterol. In contrast, the risk was negatively correlated with estimated GFR.

Most risk factors identified in this population consist of modifiable factors; however, when ignored, may result in health problems with high social and economic impact. In this sense, actions aimed at health education should be

included with more emphasis on the agenda of services of PCH teams.

These findings reinforce the importance of continuous and longitudinal health practices directed to the male population, focusing on the reduction of CVR. In addition, new studies correlating the lifestyle and health behaviors with CVR factors in different regional and care contexts are needed, to justify the development of effective public policies.

Finally, this study stresses out the potential of the FRS as a tool for stratifying the CVR in hypertensive patients attending PHC centers, aiming at improving the management and promoting high-quality care to these paients.

Author contributions

Conception and design of the research: Moreira TR, Silva LS, Cotta RMM. Acquisition of data: Silva LS. Analysis and interpretation of the data: Moreira TR, Toledo LV, Mendonça ET. Statistical analysis: Moreira TR. Writing of the manuscript: Toledo LV, Mendonça ET, Colodette RM. Critical revision of the manuscript for intellectual content: Moreira TR, Colodette RM, Silva LS, Cotta RMM.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Universidade Federal de Viçosa* under the protocol number 044/2012. 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. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al; American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics—2015: update a report from the American Heart Association. Circulation. 2015;131(4):e29-e322.
2. 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. 2ª. ed. São Pauilo: Manole; 2015. p. 780-5.
3. Brasil. Ministério da Saúde. Estratégias para o cuidado da pessoa com doença crônica: hipertensão arterial sistêmica. Brasília: Ministério da Saúde, 2013. (Cadernos de Atenção Básica, n. 37).
4. Reis APA, Pimenta TR, Rossi VEC, Maia MAC, Andrade RD. Hipertensão Arterial e Diabetes Mellitus: sistematização da assistência através da consulta de enfermagem em uma Unidade Escola do Programa de Saúde da Família. Ciência et Praxis. 2014; 7(13): 55-62.
5. Pimenta HB, Caldeira AP. Cardiovascular risk factors on the Framingham Risk Score among hypertensive patients attended by family health teams. Ciênc. saúde coletiva. 2014 Jun; 19(6): 1731-1739.
6. Cichocki M, Fernandes KP, Castro-Alves DC, Gomes MVM. Physical activity and modulation of cardiovascular risk. Rev Bras Med Esporte. 2017 Fev; 23(1): 21-25.
7. SBC. Sociedade Brasileira de Cardiologia. Departamento de Hipertensão Arterial. VII Diretrizes brasileiras de hipertensão. Rev Bras Hipertens. 2016;107(3)supl3:1-103.
8. Matsudo S, Araújo T, Matsudo V, Andrade D, Andrade E, Oliveira L, Braggion G. Questionário Internacional De Atividade Física (IPAQ): Estudo de validade e reprodutibilidade no Brasil. Rev Bras Ativ Saude. 15out.2012;6(2):5-8.
9. Jelliffe DBI. Evaluación del estado de nutrición de la comunidad. Genebra: OMS; 1968.
10. World Health Organization.(WHO). Obesity: Preventing and managing the global epidemic. Report of a WHO Consulation on Obesity. Geneva; 2000.
11. Lipschitz DA. Screening for nutritional status in the elderly. Prim Care, v. 21, n.1, p. 55-67, 1994.
12. KDIGO. Kidney Disease Improving Global Outcomes. CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl.2013;3(1):1-150.
13. Girman CJ, Rhodes T, Mercuri M, Pyörälä K, Kjeshus J, Pedersen TR, et al. The metabolic syndrome and risk of major coronary events in the Scandinavian Simvastatin Survival Study (4S) and the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS). Am J Cardiol. 2004;93:136-41.
14. Brasil. Ministério da Saúde. Secretaria de Vigilância em Saúde. Departamento de Vigilância de Doenças e Agravos não Transmissíveis e Promoção da Saúde. Vigitel Brasil 2016: vigilância de fatores de risco e proteção para doenças crônicas por inquérito telefônico: estimativas sobre frequência e distribuição sociodemográfica de fatores de risco e proteção para doenças crônicas nas capitais dos 26 estados brasileiros e no Distrito Federal em 2016. Brasília;2017.
15. Malta DC, Bernal RTI, Andrade SSCA, Silva MMA, Velasquez-Melendez G. Prevalence of and factors associated with self-reported high blood pressure in Brazilian adults. Rev Saúde Pública. 2017; 51(Suppl 1): 1-11.

16. Britto RPA,Florencio TM, Costa ACS, Pinheiro ME. Baixa estatura, obesidade abdominal e fatores de risco cardiovascular em mulheres. Rev Bras Med. 2011; 68(3):1-4.

17. Paula EA, Paula RB, Costa DMN, Colugnati FAB, Paiva, EP. Cardiovascular risk assessment in hypertensive patients. Rev Latino-Am Enfermagem. 2013; 21(3):820-7.

18. Martin RSS, Godoy Ilda, Franco RJS, Martin LC, Martins AS. Influência do nível socioeconômico sobre os fatores de risco cardiovascular. J Bras Med. 2014; 102(2):34-7.

19. Soares-Miranda L, Siscovick DS, Psaty BM, Longstreth Jr WT, Mozaffarian D. Physical Activity and Risk of Coronary Heart Disease and Stroke in Older Adults The Cardiovascular Health Study. Circulation. 2016;133(2):147-55.

20. Nascimento ES, Branco MPFC, Moreira AKF, Hazime FA. Estratificação do risco cardiovascular global em hipertensos atendidos numa unidade de saúde da família de Parnaíba, Piauí. Rev Bras Promoç Saúde, Fortaleza. 2012; 25(3):287-94

21. Freitas RS, Fonseca MJM, Schmidt MI, Molina MCB, Almeida MCC. Fenótipo cintura hipertrigliceridêmica: fatores associados e comparação com outros indicadores de risco cardiovascular e metabólico no ELSA-Brasil. Cad Saúde Pública. 2018;34(4):e00067617.

22. Ferreira CCC, Peixoto MRG, Barbosa MAB, Silveira EA. Prevalence of cardiovascular risk factors in elderly individuals treated in the Brazilian Public Health System in Goiânia. Arq Bras Cardiol 2010; 95(5): 621-8.

23. Silva SSBE, Oliveira SFSB, Pierin AMG. The control of hypertension in men and women: a comparative analysis. Rev Esc Enferm USP. 2016;50(1):50-8.

24. Pierin AMG, Marroni SN, Taveira LAF, Benseñor IJM. Hypertension control and related factors at primary care located in the west side of the city of São Paulo, Brazil. Cien Saude Colet 2011; 16(Supl. 1):1389- 400.

25. Mendes LMO, Barros JST, Batista NNLAL, Silva JMO. Fatores associados a não adesão ao tratamento da hipertensão arterial sistêmica: uma revisão integrativa. Rev Univap. 2014; 20(35):56-68.

26. Peters SA, Singhateh Y, Mackay D, Huxley RR, Woodward M. Total cholesterol as a risk factor for coronary heart disease and stroke in women compared with men: A systematic review and meta-analysis. Atherosclerosis. 2016 May;248:123-31.

27. Nogueira JS, Melo LPL, Sousa SMA, Dias RS, Silva LDC. Fatores de risco cardiovascular e doença coronariana: uma análise em pacientes revascularizados. Rev Pesq Saúde. 2016;17(1):37-41.

28. Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC. Uncontrolled and Apparent Treatment Resistant Hypertension in the United States, 1988 to 2008. Circulation 2011; 124(9):1046-58.

29. Go AS, Chertow GM, Fan D, Mcculloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-305.

30. Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, et al. Cardiovascular disease risk status in elderly persons with renal insufficiency. Kidney Int. 2002;62(3):997-1004.

31. Manjunath G, Tighioaurt H, Coresh J, Macleod B, Salem DN, Griffith JL, et al. Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. Kidney Int. 2003;63(3):1121-9.

32. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Atenção Especializada e Temática. Diretrizes Clínicas para o Cuidado ao paciente com Doença Renal Crônica – DRC no Sistema Único de Saúde. Brasília;2014.

33. Rio de Janeiro (ESTADO). Superintendência de Atenção Primária. Prefeitura do Rio de Janeiro. Referência Rápida. Prevenção cardiovascular. [Citado em 2018 mar 18]. Disponível em:http://www.rio.rj.gov.br/dlstatic/10112/4446958/4111922/GuiaCardio.pdf

34. Dias EG, Souza ELS, Mishima SM. Contribuições da Enfermagem na adesão ao tratamento da hipertensão arterial: uma revisão integrativa da literatura brasileira. R Epidemiol Control Infec, Santa Cruz do Sul.2016;6(3):138-44.

35. Costa JMBS, Silva MRF, Carvalho EF. The implementation analysis of the arterial hypertension care by the Family Health teams in Recife city (Pernambuco, Brazil). Cien Saude Colet. 2011;16(2):623-33.

International Journal of Cardiovascular Sciences. 2020; 33(3):225-226

EDITORIAL

The Importance of Cardiovascular Risk in Primary Healthcare

Erika Maria Gonçalves Campana[1] and Rafael Santos Costa[1,2]

Universidade Iguaçu,[1] Rio de Janeiro, RJ – Brazil.
Universidade do Estado do Rio de Janeiro,[2] Rio de Janeiro, RJ – Brazil.

Cardiovascular Diseases (CVDs) are the leading cause of death in Brazil and worldwide, determining increased morbidity and disability-adjusted life years. The implementation of health policies, among them, encouraging healthy lifestyle habits and providing access to primary and secondary CVD prevention measures, associated with the treatment of cardiovascular (CV) events are essential to control CVD in all countries, including Brazil.[1]

Arterial hypertension (AH) has a high prevalence in Brazil. It varies according with the population studied and the assessment method used. It is often associated with metabolic disorders, functional and/or structural changes in target organs, being worsened by the presence of other risk factors (RF), such as dyslipidemia, abdominal obesity, glucose intolerance and diabetes mellitus (DM).[2]

For an individualized approach of hypertensive patients, the Ministry of Health proposes the use of risk stratification to define the prognosis and clinical approach to hypertension in primary health care (PHC), including the adoption of the Framingham risk score (FRS).[3] This score includes the estimate of 10 years of coronary and cerebrovascular events, peripheral arterial disease, or heart failure (HF) and was also the score adopted by the Department of Atherosclerosis of SBC (Departamento de Aterosclerose da Sociedade Brasileira de Cardiologia - SBC-DA).[1]

Published studies have shown that, worldwide, over the past 50 years, the population has increased in weight. This is an important cardiovascular risk and should be tackled through a government policy in pursuit of an effective action.[4]

A study carried out in Northern Brazil on the prevalence of cardiovascular risk factors in patients with coronary artery disease showed that sedentary lifestyle was present in approximately three quarters of individuals (74.4%); overweight and obesity in more than half (64.4%); and high waist circumference measurements in 88.9% of women and 51.8% of men.[5] In a study conducted in the city of Rio de Janeiro, Pizzi and cols.,[6] evaluated the association between pulse wave velocity (PWV) with some cardiovascular risk factors (blood pressure, serum lipids, insulin and HOMA-IR and adiponectin) in young individuals. The results showed that cardiovascular impairment assessed by PWV was higher among individuals with these risk factors, especially among male subjects and those with higher mean blood pressure.[6]

The study ELSA-Brasil is a multicenter cohort research performed in several Brazilian teaching and research institutions. It was designed to investigate the impact of cardiovascular risk factors (diabetes, history of CVD and its risk factors) on the morbidity, mortality and costs for the Brazilian healthcare system.[7] In a recent publication of this study, which included data from 8,449 participants aged 35 to 74 years, the authors evaluated the association between abdominal adiposity and the carotid intima-media thickness (CIMT), according to the following indicators: waist circumference (WC), waist-to-hip ratio (WHR), conicity index (C index), lipid accumulation product (LAP) and visceral adiposity index (VAI). It was clear that this association exists in both genders, mainly for waist circumference.[8] In the multiple logistic regression, the abdominal adiposity diagnosed by WC showed an important effect on the CIMT in both genders (men: OR = 1.47, 95%CI: 1.22-1.77, women: OR = 1.38; 95%CI: 1.17-1.64).

Keywords

Cardiovascular Diseases/mortality; Cardiovascular Diseases/prevention and control; Risk Factors; Hypertension; Life Style; Obesity; Treatment Adherence.

Mailing Address: Erika Campana
Av. Abílio Augusto Távora, 2134 - Dom Rodrigo, Nova Iguaçu. Postal Code: 26275-580, Nova Iguaçu, Rio de Janeiro, RJ – Brazil.
E-mail: campanaemg@predialnet.com.br, campanaemg@gmail.com

DOI: https://doi.org/10.36660/ijcs.20200074

In the ERICA (Study of Cardiovascular Risk Factors in Adolescents) study, 71,000 adolescents were evaluated in 1,248 schools of 121 Brazilian municipalities. The purpose of the study was to identify cardiovascular risk factors, such as metabolic syndrome, hypertension, physical inactivity, obesity, among others. These data provides a better understanding of issues related to the health of Brazilian adolescents, and allows for more effective public health interventions aimed at protecting this stage of life, since several of these risk factors tend to continue into adulthood.[9] Among the main study results are: high prevalence of overweight/obesity (25,5%, 95%CI: 24.4%-26.6%), high blood pressure (9.6%, 95%CI: 8.9%-10.3%) and low HDL-C (47.3%, 95%CI: 45.2%-49.3%). The prevalence of metabolic syndrome was of 2.6% (95%CI: 2.3%-2.9%). In addition, more than half of the adolescents reported a sedentary lifestyle. Regional estimates indicated the South region as the one with the highest prevalence of risk factors. The ERICA study also demonstrated an important relationship between the incidence of hypertension and obesity. In fact, the study indicated that obesity, in young populations, could explain one-fifth of the prevalence of hypertension among these adolescents.[10]

In their article published in this issue, Moreira e cols. provide data in agreement with other Brazilian samples. They search to identify the cardiovascular risk factors in hypertensive patients assisted in a primary health care center, located in a municipality of Zona da Mata, State of Minas Gerais, Brazil. The method they used included data collection, administration of questionnaires, anthropometric measurements and laboratory tests. A high cardiovascular risk was associated with male sex, number of medications used and high total cholesterol rates. An inverse correlation was observed between the glomerular filtration rate and cardiovascular risk. They also observed that most risk factors in this population were modifiable. These results show that the data are aligned with the main national and international guidelines, according to which changes in lifestyle and the implementation of public health policies can effectively correct, or at least control, these modifiable cardiovascular risk factors.

References

1. 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.
2. Malachias MVB, Souza WKSB, Plavnik FL, Rodrigues CIS, Brandão AA, Neves MFT, et al., Sociedade Brasileira de Cardiologia. 7ª Diretriz Brasileira de Hipertensão Arterial. Arq Bras Cardiol 2016;107(supl 3):1-83.
3. Moreira TR, Toledo LV, Mendonça EJ, Colodette RM, Silva L, Cotta RM - Evaluation of Cardiovascular Risk in Hypertensive Individuals Attending a Primary Health Care Center. Int J Cardiovasc Sci. 2020;33(3):225-226.
4. Jardim PCV. Excesso de peso, o risco cardiovascular do século - Arq Bras Cardiol. 2019;113(2):185-7.
5. Silveira EL, Cunha LM, Pantoja MS, Lima AVM, Cunha NA. Prevalência e distribuição de fatores de risco cardiovascular em portadores de doença arterial coronariana no Norte do Brasil - Rev Fac Ciênc Méd Sorocaba. 2018;20(3):167-73.
6. Pizzi OL, Brandão AA, Pozzan R, Magalhaes MEC, Freitas EV.Velocidade de onda de pulso no jovem . Arq Bras Cardiol. 2013;100(1):60-6
7. Brasil.Ministério da Saúde. ELSA Brasil: maior estudo epidemiológico da América Latina - Rev Saúde Pública. 2009;43(1):1-2.
8. Eickemberg M, Amorim LD, Almeida MC, Aquino EM, Fonseca MJ. e cols. - Indicadores de Adiposidade Abdominal e Espessura Médio-Intimal de Carótidas: Resultados do Estudo Longitudinal de Saúde do Adulto - ELSA-Brasil - Arq Bras Cardiol. 2019; 112(3):220-7
9. Cureau FV, Bloch KV, Schaan BD. Estudos dos Riscos Cardiovasculares em Adolescentes (ERICA): resultados e potencialidade – Ver Saúde Pública. 2016; 50 (supl 1):2s.
10. Cureau, Felipe Vogt; Bloch, Kátia Vergetti; Schaan, Beatriz D. Estudo de riscos cardiovasculares em adolescentes (ERICA): resultados principais e perspectivas. Rev Soc Cardiol Estado de São Paulo.2019;29(1):28-33.

International Journal of Cardiovascular Sciences. 2020; 33(3):227-232

ORIGINAL ARTICLE

Diagnostic and Prognostic Role of Liver Elastography in Heart Failure

Diane Xavier Ávila, Priscila Abreu Matos, Gabriel Quintino, Wolney de Andrade Martins, Dalmo Machado, Claudio Tinoco Mesquita, Humberto Villacorta Junior

Universidade Federal Fluminense, Niterói, RJ - Brazil

Abstract

Background: Hepatic congestion is a frequent finding in patients with heart failure (HF). Physical examination has limitations in quantifying systemic congestion and requires correlation with echocardiographic and laboratory data (usually B-type natriuretic peptide, BNP, or N-terminal pro-B type natriuretic peptide, NT-proBNP). Hepatic elastography evaluates liver stiffness using a transducer that transmits low-frequency vibrations (50 Hz), and the speed of shear waves propagating through the tissues is measured by ultrasound. The faster the vibrations propagate in the hepatic parenchyma, the stiffer the liver, which, in case of HF, can be correlated with hepatic congestion.

Objective: In this systematic review, case-controls, cohort studies, and randomized clinical trials were searched in MEDLINE, LILACS and Cochrane Database of Systematic Review, to evaluate the use of elastography in the detection of hepatic congestion in patients with HF.

Methods: From the 49 articles retrieved, seven were selected for review, according to the inclusion and exclusion criteria. The most used methods for the diagnosis and evaluation of HF were echocardiography combined with BNP and NT-proBNP measurements.

Results: Elastography performed at bedside was able to establish a significant correlation between increased liver stiffness and increased venous capillary pressure. In addition, liver elastography performed at hospital discharge was able to predict rehospitalization and mortality.

Conclusion: Liver elastography is a non-invasive method that can be useful in predicting prognosis and mortality of individuals with HF, contributing to the clinical management of these patients. (Int J Cardiovasc Sci. 2020; 33(3):227-232)

Keywords: Heart Failure/physiopathology; Heart Failure/mortality; Hepatic Congestion; Elastography; Ultrassonography/methods; Echocardiography/methods; Hospitalizartion; Humans.

Introduction

Heart failure (HF) is a highly prevalent syndrome, affecting 1% to 2% of the world population and more than 10% of people over 70 years of age.[1-3] In Brazil, 9.3% of people older than 45 years have HF[4] and according to the BREATHE registry (Brazilian Registry of Acute Heart Failure), hospital mortality for decompensated HF is 12.6%.[5] HF is a clinical condition characterized by signs and symptoms related to systemic hypoperfusion and capillary congestion, that affect class functional status and quality of life of individuals. With increased filling pressures and damping of blood flow, the liver is affected by congestion secondary to HF.[6-9] The impact of HF on liver function was described a long time ago, and the pathophysiological relationship is confirmed by small changes in hepatic markers even in the absence of a diagnosis of liver disease.[6] In this regard, based on the various etiologies and comorbidities in HF, it becomes relevant to know the methods for assessing hepatic congestion and the mechanisms of associated injuries.

Liver elastography is an imaging test that evaluates liver stiffness using an ultrasound transducer operating at 5 MHz. The device transmits low-frequency vibrations

Mailing Address: Diane Xavier Ávila
Universidade Federal Fluminense - Cardiologia - Rua Marquês do Paraná, 303, 6º andar. Postal Code: 24030-215, Centro, Niterói - Brazil
E-mail: dianeavilamed@gmail.com, dianeavilamed@yahoo.com.br

DOI: https://doi.org/10.36660/ijcs.20190005

Manuscript received January 07, 2019; revised manuscript April 24, 2019; accepted August 07, 2019.

(50 Hz) and the speed of shear waves propagating through the tissues is measured by ultrasound. The stiffer the hepatic parenchyma, the faster the vibrations are propagated. The waves are measured in kiloPascals (kPa), and this measure may correlate with hepatic congestion. The transducer is placed in the intercostal space at the intersection of the mid-axillary line and a transverse line at the level of the xiphoid process. The result of the elastography represents the average of all valid acquisitions and varies from 2.5 to 75 kPa. Elastography is reliable when all these criteria are met: 10 valid measurements, an interquartile range (IQR) < 30% of the average and a success rate > 60%. Two transducers are available: the standard "M" probe, used in non-obese patients, and the "XL", used for obese patients or when the results produced by the M probe are unreliable. The reference value of elastography in healthy subjects is around 5.5 kPa with the M transducer.[7]

With the aging of the population, an increase in the incidence of HF is expected. Advances in medicine and in the treatment of cardiovascular diseases will increase life expectancy, and consequently, the number of elderly individuals will also increase.[6] Thus, with the increasing trend of the prevalence of HF, there is a growing need for methods that facilitate the management of these patients, mainly because subclinical congestion is a common cause of early rehospitalization in HF.

The objective of this study was to evaluate the use of elastography in the detection of hepatic congestion in patients with HF in different clinical settings, and its prognostic role in these patients.

Methods

A systematic review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[10] The inclusion criteria of the studies were: articles written in English or Portuguese that included hepatic elastography in the assessment of congestion in patients with HF. Data were extracted in a standardized manner by two independent investigators, who were also responsible for evaluating the methodological quality of the manuscripts. Articles in duplicate, review studies, editorials, letters to the editor and experimental studies in animals were excluded. The search in the literature was conducted in June 2018, with no limit of publication date.

Case controls, cohort studies and randomized clinical trials were searched in MEDLINE, LILACS, Scielo databases and Cochrane Database of Systematic Review. The descriptors and respective connectors used in PubMed were "elastography" [All Fields] AND "heart failure" [All Fields], with 44 articles retrieved; the descriptors used in BIREME were "elastography" AND "heart failure" AND (Collection:("06-National/BR" OR "05-specialized") OR db: ("LILACS" OR "MEDLINE") AND (Collection: ("06-National/BR" OR "05-specialized") OR db: ("LILACS" OR "MEDLINE")) AND (MJ: ("imaging techniques by Elasticity" OR "heart failure") AND Type_of_study: ("case_control "OR "cohort") and limit: ("humans") and La: ("en"), with identification of five more articles; and the terms used in the search in Cochrane were "elastography " AND "heart failure", and no articles available were found. Then, a total of 49 articles were retrieved.

The selection of the articles was made in two stages. In the first stage, two independent authors read the abstracts and those that did not fit the inclusion criteria were excluded. In the second stage, the remaining studies were read in full and, similarly, those that did not meet the inclusion criteria according to the PRISM 10 model were excluded (Figure 1). At the end, seven articles were included in the review.

Results

This systematic review aimed to identify the scientific evidence on the use of elastography in HF. The results showed an important correlation between liver stiffness and markers of increased venous capillary pressure.[7,10-13] In addition, liver elastography performed at hospital discharge was able to predict rehospitalization and mortality.[13]

In the seven selected articles, patients were evaluated in the hospital and there was a variation in the number of study participants. The most commonly used methods for the diagnosis and evaluation of HF were echocardiography in conjunction with measurements of B-type natriuretic peptide (BNP) or N-terminal pro-B type natriuretic peptide (NT-proBNP). However, no standardization of these methods was found in most of these articles. There was a low variation in the cutoff values of elastography and some authors reported a range for normal and abnormal values (Table 1). All studies showed a correlation between increased liver stiffness and elevation of BNP or NT-ProBNP levels in the admission.[1,11,12]

Colli et al.[14] observed that most patients with acute HF had liver stiffness values and NT-proBNP levels that

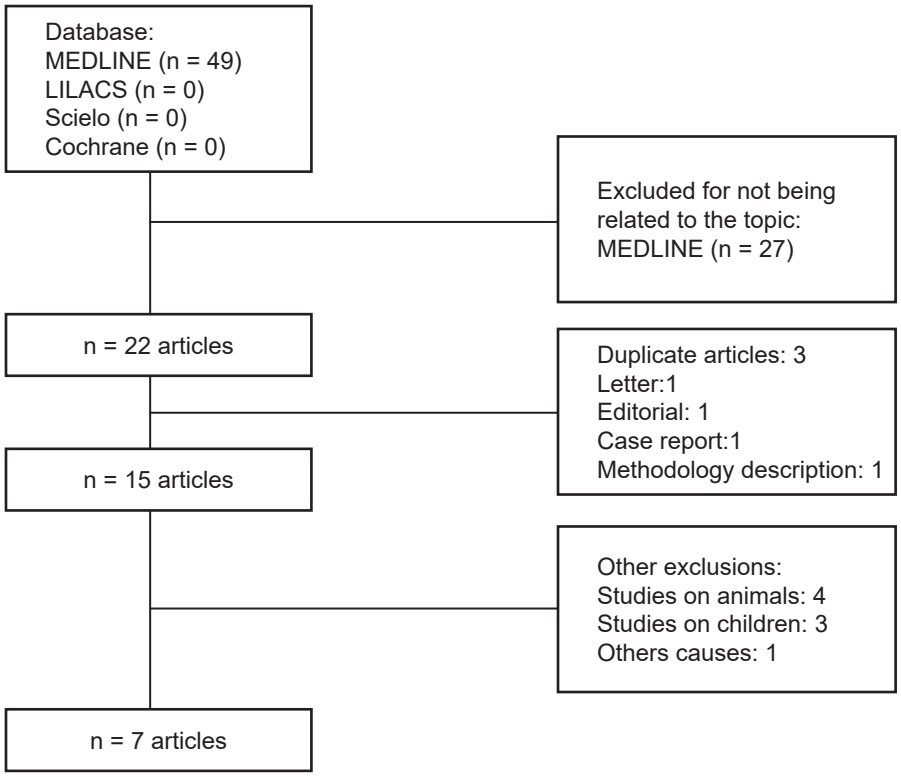

Figure 1 - Flowchart of study selection following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

tended to decrease with clinical improvement. Natriuretic peptides are released in response to volume overload and increased pressure in cardiac cavities and their levels reflect systolic and diastolic functions, as well as right ventricular function.[14]

Nishi et al.[11] found that liver stiffness correlated with preoperative severity in patients with severe HF and reflected hepatic congestion and may be useful in predicting right atrial pressure measurement and post-operative complications in patients who underwent left ventricular assist device implantation. This was the first study to measure the variation of liver stiffness and its relationship with clinical outcome and laboratory data, including BNP levels.[11] Lindvig et al.[13] observed a high value of liver stiffness at admission associated with increased mortality, hepatic cirrhosis and congestive HF, with a mortality rate of 20.8% in patients with transient elastography greater than 8.0 kPa. Taniguchi et al.[12] suggested liver stiffness as a systemic volume index and predictor of HF severity, similarly to Alegre et al.,[7] who also reported an association of hepatic congestion with worsening of patient outcome.

An important finding of these reports was the fact that the volume withdrawal by diuretic therapy or hemodialysis did not alter the values of elastography at short time.[7] Another study showed an improvement in elastographic values even though they did not reach standards of normality after cardiac decompensation.[14]

Discussion

Increased filling pressure of the right cavities can result in venous congestion, which is considered a determinant factor for systemic injury, cirrhosis and death.[8,11] Elastography is a method that has been recently used to evaluate hepatic congestion. It is a painless, quick (< 10 minutes in the bedside), safe examination, and that has a good acceptance by patients, especially in case of repeated examinations.[15]

Despite increasing evidence of the benefits of this method in the management of patients with HF, elastography is still little explored. The cutoff values of BNP and NT-proBNP for the diagnosis of acute HF have

Table 1 - Summary of the results of the studies included in this systematic review

Authors	Number of patients	Male	BNP (pg/mL)	NT-proBNP (pg/mL)	p-value	Elastography
Saito et al. 2018	105	73	-	5.175 (IQR. 2.586-11.1695) in patients with < 8.8 kPa; 5.432 (IQR. 2.338-11.527) in patients with > 8.8 kPa	0.052 (< 0.05)	Low (< 8.8 kPa) - 52 patients. High (> 8.8 kPa) - 53 patients
Taniguchi et al. 2018	171	116	199 (tertile 91-356)	-	0.019 (< 0.05)	5.6 kPa (average). > 6.9 kPa in patients with estimated right atrial filling pressure > 7.1 mmHg
Nishi et al. 2015	30	21	844 ± 806 (Standard deviation)	-	-	13.3 kPa. preoperative > 7.0kPa with atrial-ventricle assistance (AVD); > 12.5 kPa correlated with postoperative death
Alegre et al. 2013	26	-	-	1,511 versus 3,535 (CHF vs AHF at admission, respectively); decrease from 3,535 pg/ml to a median of 1,098 pg/ml at discharge (after clinical compensation)	0.025 (< 0.05)	6.5 vs 14.4 kPa (p = 0.009) in admission and 8.2 kPa in hospital discharge (p = 0.008)
Hopper et al. 2012	116	61	-	4596 +- 4237 (Standard deviation)	-	Healthy individuals n = 55. 4.4 kPa (percentile 25 – 3.6. percentile 75- 5.1); individuals with left heart disfunction 4.7 (4.0. 8.0) kPa (p = 0.04) Stable HF 9.7 (5.0. 10.8) kPa (p < 0.001) Decompensated HF 11.2 (6.7. 14.3) kPa (p < 0.001)
Lindvig et al. 2012	289	289	-	-	-	> 8.0 kPa (48/212) cirrhosis and hepatic congestion; independent mortality predictor
Colli A; 2010	27	12	-	7,114 (IQR 2,939-13,437) in admission and 4,127 (IQR 947-5955) at hospital discharge, with median decrease of 3,128(IQR 1,373-6,157)	< 0.001 (< 0.05)	Admission > 7.65 kPa in 14 of 24 patients and 5 (21%) more than 13.01 kPa and 14 > 7.65 kPa at hospital discharge

BNP: B-type natriuretic peptide; NT-proBNP): N-terminal pro-B type natriuretic peptide; IQR: interquartile range; CHF compensated chronic heart failure; AHF acute decompensated heart failure.

varied considerably among the studies and have not been reported in all studies of this review, bringing difficulty to data interpretation.

There is a lack of continous parameters in the evaluation of individuals studies selected for the systematic review. Besides that, the small number of samples, reduced quantity of articles with statistical relevant power and wich relate the method to the issue of HF brings a difficulty in standardizing the assessment of the method.

The studies did not compare elastography with liver biopsy, which is the gold standard for evaluation of derangement of liver architecture. However, while biopsy is an invasive method, and hence difficult to be reproduced, elastography is a non-invasive method that can be used in different liver diseases. It is worth

mentioning, however, that liver elastography is an examiner-dependent method which requires adequate training. Furthermore, there is no standardization in the analysis of the results.

Patients with liver disease and cirrhosis have higher elastography values than patients with other chronic diseases and were then excluded from the studies to avoid confounding factors.

There was a divergence on whether liver stiffness improves with diuretic treatment compared with elastography in a short period of time, which shows the importance of a long-term follow-up, since this could have a positive impact on morbimortality. In addition, it is believed that elastography can be used as a response tool to clinical or supportive therapy, or as a prognostic tool in HF treatment.

Conclusion

Data on the use of elastography in the evaluation of patients with different stages of HF, such as stable, acute or chronic decompensated HF, and of patients undergoing left ventricular assist device implantation is still scarce and more data are needed. The method seems to increase the diagnostic power of the elevation in the filling pressures of the right cavities and, consequently, increased liver stiffness. The effects of heart disease on liver function may be silent, not detected by physical examination or laboratory tests, and in this context, elastography seems to be the ideal non-invasive method for assessing liver damage caused by cardiovascular disease. This analysis can help in the clinical management of these patients and be of prognostic value at hospital discharge.

Author contributions

Conception and design of the research: Avila DX. Acquisition of data: Avila DX, Lopes GQ, Matos PA. Analysis and interpretation of the data: Avila DX, Matos PA, Martins WA, Villacorta H, Mesquita CT, Machado D. Statistical analysis: Avila DX, Machado D. Writing of the manuscript: Avila DX, Matos PA. Critical revision of the manuscript for intellectual content: Avila DX, Martins WA, Villacorta H, Mesquita CT.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of master submitted by Diane Xavier de Ávila, from Fluminense Federal University.

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. Ceia F, Fonseca C, Mota T, Morais H, Matias F, de Sousa A, et al. Prevalence of chronic heart failure in Southwestern Europe: the EPICA study. Eur J Heart Fail. 2002;4(4):531-9.
2. Redfield MM, Jacobsen SJ, Burnett JC Jr, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. JAMA. 2003;289(2):194-202.
3. Bleumink GS, Knetsch AM, Sturkenboom MC, Straus SM, Hofman A, Deckers JW, et al. Quantifying the heart failure epidemic: prevalence, incidence rate, lifetime risk and prognosis of heart failure The Rotterdam Study. 2004;25(18):1614-9.
4. Jorge AJL, Rosa MLG, Fernandes LCM, Freire MDC, Correia DMS, Rodrigues RC, et al. Heart failure prevalence study among patients enrolled in the family health program, Niterói. The DIGITALIS Study: design and method. Rev Bras Cardiol. 2011;24(5):320-5.
5. Albuquerque DC, Neto JD, Bacal F, Rohde LE, Bernardez-Pereira S, Berwanger O, et al. I Brazilian Registry of Heart Failure - clinical aspects, care quality and hospitalization outcomes. Arq Bras Cardiol. 2015;104(6):433-42.
6. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in Prevalence and outcome of heart failure with preserved ejection fraction. N Eng J Med. 2006;355(3):251-9.
7. Alegre F, Herrero JI, Iñarrairaequi M, Gavira JJ, Pujol C, Montero A, et al. Increased liver stiffness values in patients with heart failure. Acta Gastroenterol Belq. 2013;76(2):246-50.
8. Hopper I, Kemp W, Porapakkham P, Sata Y, Condon E, Skiba M, et al. Impact of heart failure and changes to volume status on liver stiffness: non-invasive assessment using transient elastography. Eur J Heart Fail. 2012;14(6):621-7.

9. Saito Y, Kato M, Nagashima K, Monno K, Aizawa Y, Okumura Y, et al. Prognostic relevance of liver stiffness assessed by transient elastography in patients with acute decompensated heart failure. Circ J. 2018;82(7):1822-9.

10. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015 Jan 1;4:1.

11. Nishi H, Toda K, Miyagawa S, Yoshikawa Y, Fukushima S, Kawamura M, et al. Novel method of evaluating liver stiffness using transient elastography to evaluate perioperative status in severe heart failure. Circ J. 2015;79(2):391-7.

12. Taniguchi T, Ohtani T, Kioka H, Tsukamoto Y, Onishi T, Nakamoto K, et al. Liver stiffness reflecting right-sided filling pressure can predict adverse outcomes in patients with heart failure. JACC Cardiovasc Imaging. 2019;12(6):955-64.

13. Lindvig K, Mössner BK, Pedersen C, Lillevang ST, Christensen PB. Liver stiffness and 30-day mortality in a cohort of patients admitted to hospital. Eur J Clin Invest. 2012;42(2):146-52.

14. Colli A, Pozzoni P, Berzuini A, Gerosa A, Canovi C, Molteni EE, et al. Decompensated chronic heart failure: increased liver stiffness measured by means of transient elastography. Radiology. 2010;257(3):872-8.

15. Perazzo H, Veloso VG, Grinsztejn B, Hyde C, Castro R. Factors that could impact on liver fibrosis staging by transient elastography. Int J Hepatol. 2015;2015:624596.

International Journal of Cardiovascular Sciences. 2020; 33(3):233-234

EDITORIAL

Hepatic Elastography in the Assessment of Heart Failure: Where We Came from and Where We Are Going

Edison Migowski

Hospital Universitário Clementino Fraga Filho – UFRJ, Rio de Janeiro, RJ – Brazil

Congestive heart failure (HF) is the end stage for many cardiac diseases. It is associated with high mortality and high hospital readmission rates, despite advances in pharmacological (sacubitril-losartan, beta-blockers and renin-angiotensin system inhibitors) and non-pharmacological (defibrillators and resynchronizers) treatment.

Therefore, it is natural that clinicians are interested in the improvement of diagnostic methods and efficient prognostic markers capable of identifying patients at higher risk, thus anticipating complications and providing treatment guidance.

We cardiologists have long recognized biventricular dysfunction as a more severe and advanced form of HF, and brain natriuretic peptide (BNP) as a biochemical marker, used for both diagnostic and prognostic purposes. However, BNP are not yet widely used in daily clinical practice, probably due to overestimation of clinical parameters for the indication, conduction and determination of the therapy in most services focused on these patients' assistance.

The search for other methods with prognostic and diagnostic value for right ventricular dysfunction remains constant. Nevertheless, these methods must meet the requirements that current tests have failed to achieve: low cost, high specificity and sensitivity, reproducibility and no requirement of high technical knowledge to operate.

Elastography has long been used by hepatologists in the evaluation of liver parenchyma stiffness.[1] This test assesses tissue stiffness using an ultrasound transducer, which measures low-frequency vibrations. There is a direct relationship between the parenchyma stiffness and the propagation of these vibrations registered by the device. The stiffer the hepatic parenchyma, the faster the vibrations are propagated. Often, this stiffness is associated with numerous factors such as fibrosis, inflammation, liver perfusion, fatty infiltration, cholestasis and congestion.

Interestingly, the congestion that interfered in the results of elastography, during the investigation of liver diseases, called cardiologists' attention. It was clear that there was an important correlation between increased liver stiffness and increased venocapillary pressure[2] and also the possibility of using this test to assess right ventricular performance.

Ávila D et al.,[3] in their excellent systematic review, selected 7 studies that compared hepatic elastography (HE) with the results of echocardiography and BNP, in patients with HF. They concluded that the use of this technique seems to improve the diagnostic power of increased right-sided filling cardiac pressures and could assist in the medical management of these patients, adding prognostic value at the moment of hospital discharge. However, they were careful in stating that these are not A definitive result, and further studies are needed for a better understanding of this issue.

Elastography combined with ultrasound is a simple, fast, low-cost and noninvasive test, performed at the bedside. Still, several barriers have yet to be overcome:

Regarding elastography, the method is examiner-dependent. Besides, it requires a device so that the measurements are obtained, and adequate training to mitigate the possibility of measuring errors.

Keywords

Heart Failure; Elasticity Imaging Techniques/methods; Hospitalization; Outcomes; Patient Readmission; Prognosis; Liver Diseases.

Mailing Address: Edison Migowski
Rua Rodolpho Paulo Rocco, 255. Postal Code: 21941-590, Ilha do Fundão, Rio de Janeiro, RJ – Brazil
E-mail: emigowski@gmail.com

DOI: https://doi.org/10.36660/ijcs.20200070

Patients with liver disease and cirrhosis present higher values in HE compared to patients with cardiac disease. In general, this group was excluded from the studies that aimed at investigating patients with HF in order to avoid confounding factors. Therefore, the assessment of congestion in the presence of underlying liver disease still represents a challenge that must be overcome.

Similarly to most complementary exams, HE requires good clinical correlation, especially because it does not specify the cause of increased stiffness.

Fat tissue attenuates ultrasound wave propagation and, for this reason, obesity can make it difficult to perform the test.[4] Failure or inconsistent results can reach almost 20%. Factors associated with unreliable results include: BMI greater than 30 kg m^2, age above 52 years, female sex, inexperienced operator, type 2 diabetes mellitus and ascites. Liver inflammation and steatosis may also reduce the test's accuracy.[5-7]

Conclusion

There seems to be a consensus that the greater the liver stiffness, the greater the risk of mortality ("Stone liver, heart in danger", according to Pernot and Villemain)[8] However, innumerous studies are necessary to determine which therapeutic interventions would be capable of decreasing that stiffness and whether such decrease would have a consistent impact on prognosis. Another relevant data is that we do not know exactly the amount of information that HE can add to clinical practice, in addition to the information already provided by echocardiography and BNP.

It is believed that a long way must be taken until this technique becomes a useful tool for cardiologists, with favorable impact on the management of a disease with high morbidity, mortality and cost for the healthcare system. Nevertheless, we can state that the interpretation of results by the clinician involved in the patient's treatment will be undoubtedly crucial for its success.

References

1. Bamber J ,Cosgreve D, Dietrich CF, Fromageau J, Bojunga J, Calliada F, et al. EFSUMB guidelines and recommendations on the clinical use of ultrasound elastography. Part 1: basic principles and technology. Eur J Ultrasound.2013;34(2):169-84.
2. Taniguchi T, Sakata Y, Ohtani T, Mizote I, Takeda Y, Asano Y, et al. Usefulness of transient elastography for noninvasive and reliable estimation of right-sided filling pressure in heart failure. Am J Cardiol. 2014;113(3):552-8.
3. Ávila D, Matos PA, Quintino G, Martins WA, Machado D, Mesquita CT, et al. Diagnostic and Prognostic Role of Liver Elastography in Heart Failure. Int J Cardiovasc Sci. 2020;33(3):227-232.
4. Sandrin L, Fourquet B, Hasquenoph JM, Yon S, Fournier C, Mal F, et al. Transient elastography: a new noninvasive method for assessment of hepatic fibrosis. Ultrasound Med Biol. 2003;29(12):1705-13.
5. Arena U, Vizzutti F, Corti G, Stasi C, Bresci S, Moscarella S, et al. Acute viral hepatitis increases liver stiffness values measured by transient elastography. Hepatology. 2008;47(2):380-4.
6. Roulot D, Czernichow S, Le Clesieu H, Costes JL, Vergnaud AC, Beaugrand M. et al. Liver stiffness values in apparently healthy subjects: influence of gender and metabolic syndrome. J Hepatol. 2008;48(4):606-13.
7. Tapper, Chen E, Patel K, Bacon B, Gordon S, Lawitz E, et al. Levels of alanine aminotransferase confound use of transient elastography to diagnose fibrosis in patients with chronic hepatitis C virus infection. Clin Gastroenterol Hepatol. 2012;(8):932-7.
8. Pernot M, Villemain O. Stone Liver, Heart in Danger: Could the Liver Stiffness Assessment Improve the Management of Patients With Heart Failure? [Editorial]. JACC:Cardiovasc Imaging. 2019;12(6):965-6.

International Journal of Cardiovascular Sciences. 2020; 33(3):235-242

ORIGINAL ARTICLE

A Retrospective Study on Unfractionated Bovine Heparin Safety in On-Pump Cardiac Surgery

Fernando Antonio de Lima Torres,[1] Andressa C. B. Torres,[2] Allinson Ribeiro,[2] Cauê O. Maia,[2] Fernanda P. Almeida,[2] João Roceto,[2] Jorge A. Matkovski,[2] Matheus G. Kovalski,[2] Vanessa A. Pizato,[2] Tatiana M. G. Cordeiro[2]

Instituto de Cirurgia do Coração, Hospital Bom Jesus,[1] Ponta Grossa, Paraná, PR - Brazil
Universidade Estadual de Ponta Grossa,[2] Paraná, PR - Brazil

Abstract

Background: Heparin decreases the risks of thrombotic phenomena in extracorporeal circulation. However, it must present a robust safety profile itself, especially for bleeding. Contamination of porcine heparin demands an alternative source and consequent assessment of safety.

Objective: To evaluate the safety of unfractionated bovine heparin during on-pump cardiac surgery.

Methods: Descriptive, retrospective study, evaluating medical records from all patients who had on-pump cardiac surgery over four years. We observed the occurrence of bleeding, thrombocytopenia, postoperative vasoplegia, activated clotting time values and any other coagulation phenomena as safety profile parameters.

Results: We evaluated 204 medical records reporting the use of unfractionated bovine heparin. 66.18% of the patients presented thrombocytopenia, 1.04% presented bleeding of more than 2000 mL in the first 24 hours of the postoperative period. One patient presented clots in the surgical field. Median activated clotting time was 137 seconds at baseline, 803 seconds after the first dose of heparin and, after protamine, it returns to similar baseline values, that is, 149.5 seconds.

Conclusion: Unfractionated bovine heparin did not present unusual adverse effects and can be considered safe for on-pump cardiac surgery. (Int J Cardiovasc Sci. 2020; 33(3):235-242)

Keywords: Blood Coagulation Tests; Heparin/analysis, Heparin/chemistry, Heparin/standards; Cardiac Surgery; Safety; Extracorporeal, Circulation.

Introduction

Extracorporeal circulation (ECC) is a crucial component of cardiac surgery. Even with the progress of medicine, ECC remains a procedure with risks, including thrombotic phenomena, arrhythmia, bleeding, and neurologic disfunction.[1,2] Heparin is an anticoagulant agent routinely used with ECC. The ideal anticoagulant product must be effective, safe and easy to monitor, without significant interindividual differences. A balance must exist between heparin's efficacy (avoiding thrombotic phenomena) and safety (avoiding bleeding) in ECC.[2]

Heparin was initially isolated from dog liver. Since then, we have used different animals and tissues, such as porcine and bovine intestinal mucosa and bovine and sheep lungs.[3-5] The search for alternatives to bovine heparin started in the 1990s because of bovine spongiform encephalopathy, which had the potential to contaminate heparin with prions.[6] Currently, the exploration of heparin from alternative animal sources and the reintroduction of bovine heparin have become more relevant after contamination of unfractionated porcine heparin (UFH) with oversulfated chondroitin sulfate, leading to serious adverse effects, such as

Mailing Address: Fernando Torres
Praça Santos Andrade, 01, Centro. Postal Code: 84030-900, Ponta Grossa, PR - Brazil.
E-mail: fernandolimatorres@hotmail.com

DOI: https://doi.org/10.36660/ijcs.20190043

Manuscript received on February 02, 2019; reviewed on June 20, 2019; accepted on August 07, 2019.

anaphylactic reaction with facial edema, hypotension, tachycardia, nausea, urticaria, dyspnea, and death.[5,7,8] Unlike other countries, Brazil presented a lower risk of bovine spongiform encephalopathy and continued to use bovine heparin without significant concerns. Bovine heparin currently represents 40% of the heparin market in Brazil.[5]

Bovine and porcine heparins differ in biological and pharmacological aspects and, consequently, their effects on blood coagulation.[3,5,9,10] Most available data concerning the safety of bovine heparin comes from lung samples, which fell by the wayside with in the 1980s.[3] Heparin from bovine lung has a higher risk of heparin-induced thrombocytopenia.[9] Bovine and porcine intestinal heparin have a similar molecular weight, but different anticoagulant and antithrombotic properties (porcine has higher activity).[3,10,11] A higher dose of bovine heparin is necessary in order to achieve similar effects, and higher protamine dose for neutralization.[3,12] A study in animals suggests that bovine heparin presents higher risk of bleeding.[3]

The use of bovine UFH is on the rise, and more data concerning safety in humans is needed. This observational study reports the safety profile of bovine UFH in patients undergoing on-pump cardiac surgery.

Methods

This study was performed following Good Clinical Practices and in compliance with the Declaration of Helsinki of 1975, revised in 2008. The local Institutional Review Board approved the study protocol.

We performed a single-center, descriptive, retrospective investigation using data collection from all patients who had on-pump cardiac surgery, using bovine UFH (supplied by Eurofarma Laboratories S.A.) between October 2008 and November 2012 and porcine UFH (supplied by Cristália and Blausiegel Laboratories) between June 2013 and December 2014 at the Heart Surgery Institute of Hospital Bom Jesus in Ponta Grossa, Paraná, Brazil.

Patients were excluded from the study if they had received intravenous UFH two hours before the surgical procedure, and/or low molecular weight heparin or fondaparinux subcutaneously or oral anticoagulants within 12 hours before the surgical procedure, and/or fibrinolysis 48 hours before the surgical procedure. They were also not included in the absence of preoperative platelet count results, and/or cardiac surgery performed in the presence of severe sepsis, with high risk of widespread intravascular coagulation.

Eligible patient data were collected from medical records by trained reviewers under the investigator's supervision and were anonymized and stored in an electronic database instrument mainly designed for this purpose. Pre and postoperative data were collected, and the postoperative period was covered until hospital discharge or the seventh postoperative day, whichever occurred first. A questionnaire for assessing the quality of the records was also filled out for each medical history reviewed.

Study outcomes were bleeding, thrombocytopenia defined as platelets counts lower than 150,000), postoperative vasoplegia, activated clotting time (ACT) shorter than 400 seconds and coagulation phenomena, such as blood clotting with bovine UFH. Data on porcine UFH were also collected only as exploratory means.

Statistical analyses

The present study is a preliminary study of the feasibility of a descriptive nature only. We did not calculate the sample size because it was an exploratory study. Therefore, we considered all patients who met the inclusion criteria. All descriptive analyses were stratified by period in which each type of heparin was used in our service (October 2008 to November 2012: bovine UFH, and June 2013 to December 2014: porcine UFH).

Continuous variables were described by the number of participants evaluated. Mean and standard deviation and median and values range observed or quartiles Q1 and Q3, according to their distribution defined by the Shapiro-Wilk test, with alpha level of 0.05. Categorical variables were summarized by frequency distribution. The 95% confidence intervals (95% CI) were calculated for the one-time estimates.

Results

From 2008 to 2014, 790 patients underwent surgery at our medical service. Of these, we considered 428 (54.2%) for analysis (completed medical record), and 269 (62.9%) were eligible for the study, meeting inclusion and exclusion criteria. Of the patients, 75.8% were treated with bovine UFH and 24.2% were treated with porcine UFH.

Data from bovine and porcine heparin are presented in the Tables together; however, we did not compare the groups since it was not the study objective.

Male patients were more than half, with median age of 61.6 years and approximately 46% presented comorbidity. Hypertension was the most frequent comorbidity, followed by diabetes mellitus and dyslipidemia. Coronary artery insufficiency was the primary cause of the cardiovascular diagnoses that led to the surgical procedure (Table 1).

As shown in Table 2, more than 50% of the surgeries were coronary artery bypass grafting followed by aortic valve replacement. Median surgery duration was 297.5 minutes, of which ECC was 89.0 minutes.

Safety outcomes of bovine UFH patients

From the 269 medical records evaluated of patients treated with bovine UFH, the median bleeding for 24h of the postoperative period was 545 mL. Two patients (1.04%) showed bleeding of more than 2000 mL in the first 24 hours (Table 3). The incidence of thrombocytopenia was 66.18%. The need for surgical re-exploration (by bleeding or tamponade) occurred in 0.98% of the patients. No patient presented vasoplegia. One patient presented clots in the surgical field during ECC. He also presented intraoperative thrombosis of vascular grafts.

Safety outcomes of porcine UFH patients

Median bleeding after 24h was 400 mL. Two (3.07%) participants treated with porcine UFH showed bleeding of more than 2,000 mL (Table 3). Thrombocytopenia occurred in 83.08% of the patients, and surgical re-exploration was required (by bleeding or tamponade) in 3.07%. One patient presented vasoplegia, and another one had clots in the surgical field during ECC.

Table 1 - Demographic data and clinical characteristics of the study population

		Bovine UFH treated N = 204	Porcine UFH treated N = 65	Total N = 269
Gender	Male	132 (64.71)	37 (56.92)	169 (62.83)
	Female	72 (35.29)	28 (43.08)	100 (37.17)
Age (years)	Median	61.4	61.8	61.6
	(Min-max)	(16.8-87.0)	(18.1-77.1)	(16.8-87.0)
Weight (kg)	Median	72.5	73.0	73.0
	(Min-max)	(43.0-130.0)	(50.3-113.0)	(43.0-130.0)
Main comorbidities				
Hypertension		150 (73.53)	51(78.43)	201 (74.72)
Diabetes mellitus		55 (26.96)	24 (36.92)	79 (29.37)
Dyslipidemia		9 (4.41)	11 (16.92)	20 (7.43)
Main surgical indication				
Coronary artery insufficiency		134 (65.69)	39 (60.0)	173 (64.31)
Aortic stenosis		22 (10.78)	16 (24.62)	38 (14.13)
Aortic valve insufficiency		25 (12.25)	10 (15.38)	35 (13.01)
Mitral valve insufficiency		27 (13.24)	5 (7.69)	32 (11.90)
Cardiac aneurysm		15 (7.35)	5 (7.69)	20 (7.43)
Acute myocardial infarction		12 (5.88)	2 (3.08)	14 (5.20)

Qualitative variables are shown as n (%) and quantitative variables as median and minimum and maximum values. Source: prepared by the authors.

Table 2 - Surgery characteristics

		Bovine UH treated N = 204	Porcine UH treated N = 65	Total N = 269
Most frequent type of surgery				
Coronary artery bypass grafting		111 (54.41)	27 (41.54)	138 (51.30)
Aortic valve replacement		20 (9.80)	12 (18.46)	32 (11.90)
Coronary artery bypass grafting and aortic valve replacement		11 (5.39)	8 (12.31)	19 (7.06)
Mitral valve replacement		10 (4.90)	6(9.23)	16 (5.95)
Left ventricular aneurysmectomy and coronary artery bypass grafting		9 (4.41)	1 (1.54)	10 (3.72)
Atrioseptoplasty (correction of interatrial communication)		2 (0.98)	2 (3.08)	4 (1.49)
Bentall D'Bono surgery		3 (1.47)	1 (1.54)	4 (1.49)
Coronary artery bypass grafting and aortic valve replacement and mitral valve replacement		4 (1.96)	0	4 (1.49)
Mitral valve repair		3 (1.47)	0	3 (1.12)
Surgery duration	Median	297.5	230.0	270.0
	Min–max	(120–540.0)	(100.0–475.0)	(100.0–540.0)
	Q1–Q3	240.0–330.0	180.0–255.0	222.0–330.0
ECC duration	Median	89.0	86.0	88.0
	Min–max	(35.0–273.0)	(30.0–169.0)	(70.0–110.0)
	Q1–Q3	72.0–111.0	69.0–110.0	70.0–110.0

Qualitative variables are shown as n (%) and quantitative variables as median, minimum and maximum values, interquartile range. Duration is shown as minutes. Q1: percentile 25%; Q3: percentile 75%. ECC: extracorporeal circulation. Source: prepared by the authors.

Activated clotting time (ACT) values

Table 4 shows the median ACT before, during and after ECC (after protamine administration) in both groups.

Heparin dosage

Patients received a median dose of 288 mg bovine UFH before ECC, ranging from 120 to 520 mg. The total dose used ranged from 172 mg to 550 mg, with a median of 320 mg. Patients treated with porcine UFH received initial doses between 124 mg and 452 mg, with a median dose of 288.5 mg. The total dose ranged from 200 to 454 mg, with a median dose of 317 mg.

Protamine dosage

In the group treated with bovine UFH, the initial dose of protamine administered ranged from 65 mg to 900 mg, with a median dose of 500 mg. Some patients (23.5%) received an additional dose of protamine with a median dose of 100 mg, ranging from 50 to 600 mg.

For participants receiving porcine UFH, the initial protamine dose ranged from 300 to 700 mg, with a median dose of 500 mg, with an additional treatment in 35.4% of patients (median dose of 100 mg, ranging from 50 to 200 mg).

Discussion

Heparin is the anticoagulant routinely used during ECC with the advantage of lower allergy risk and an easily reversible effect through protamine.[13] However, bleeding is the most known, severe and expected adverse effect. Excessive postoperative bleeding generates higher incidence of infectious complications and higher

Table 3 - The volume of post-surgery bleeding from the thoracic drain

		Bovine UH treated N = 204	Porcine UH treated N = 65	Total N = 269
Externalized blood volume in 2h (mL)	Median (min–max)	50.0 (0.0–2,350.0)	0.0 (0.0–1,400.0)	50.0 (0.0–2,350.0)
	Q1–Q3	0.0–150.0	0.0–50.0	0.0–100.0
Externalized blood volume in 12h (mL)	Median (min–max)	250.0 (0.0–9,650.0)	250.0 (0.0–3,000.0)	250.0 (0.0–9,650.0)
	Q1–Q3	150.0–500.0	100.0–450.0	150.0–500.0
Externalized blood volume in 24h (mL)	Median (min–max)	545.0 (0.0–3,150.0)	400.0 (50.0–3,950.0)	510.0 (0.0–3,950.0)
	Q1–Q3	300.0–800.0	300.0–750.0	300.0–800.0
Postoperative externalized blood volume	Median (range)	695.0 (0.0–3,350.0)	800.0 (50.0–4,525.0)	700.0 (0.0–4,525.0)
	Q1–Q3	425.0–1,012.5	400.0–1,100.0	400.0–1,050.0

Quantitative variables as median (minimum-maximum values) and interquartile range. Q1: percentile 25%; Q3: percentile 75%. Postoperative period: 24-hour period beginning at 7 o'clock in the morning of the day following the day of surgery. Source: prepared by the authors.

Table 4 - Activated clotting time (ACT) values

		Bovine UH treated N = 204	Porcine UH treated N = 65
ACT at baseline	Median (min–max)	137.0 (66.0–470.0)	140.5 (80.0–.0)
Pre-ECC	Median (min–max)	803.0 (324.0–2,000.0)	693.0 (440.0–2,000.0)
ECC: 1st hour dose	Median (min–max)	620.0 (155.0–1,800.0)	585.0 (126.0–1,100.0)
ECC: 2nd hour dose	Median (min–max)	591.0 (392.0–991.0)	1365.0 (150.0–2,000.0)
ECC: 3rd hour dose	Median (min–max)	638.5 (392.0–885.0)	513.0 (489.0–537.0)
ACT after protamine	Median (min–max)	149.5 (63.0–307.0)	154.0 (95.0–460.0)

Results are shown in seconds. Median (minimum–maximum). ACT: Activated clotting time. ECC: extracorporeal circulation. Source: prepared by the authors.

mortality, among other complications.[14] Heparin-induced thrombocytopenia is also a severe adverse effect, occurring in 5 to 7 days after continuous use of the drug, increasing the risk of thrombotic phenomena.[15] Therefore, heparin safety must be well established.

In this preliminary, descriptive, exploratory, retrospective investigation, thrombocytopenia was the most frequent blood dyscrasia found after surgery using bovine UFH. Postoperative thrombocytopenia in cardiovascular surgery with ECC is expected and usually temporary.[16] Apart from ECC, it can be related to multiple factors including the patient's age, previous predisposition, surgery duration, type of surgery, need for reoperation, intraoperative and postoperative blood loss, heparin dose, heparin reversibility, hypothermia, circulatory arrest, and low cardiac output.[16,17] Heparin-induced thrombocytopenia is also a possibility, but it needs laboratory confirmation with the presence of heparin-dependent cell-activating anti-PF4/heparin antibodies.[18] In our study, patients undergoing more complicated and prolonged surgery presented blood dyscrasia with bovine UFH, with a higher risk of bleeding, such as Bentall- and D' Bono surgery (aortic root reconstruction with valve tube and replantation of coronary ostia), two coronary artery bypass grafting surgeries, mitral-aortic valve replacement with coronary artery bypass grafting, mitral-aortic valve replacement, and aortic valve replacement. The literature reports that the duration of ECC is directly related to the risks.[1,16,19,20]

The main comorbidity in cardiac surgery is postoperative bleeding.[20] Published results are highly variable as to what is considered an "acceptable" volume of postoperative bleeding. Miana et al.,[20] consider 150 mL/hour to be significant postoperative bleeding.[20] According to the Kirklin/Barratt-Boyes table,[21] maximum drainage of 500 ml is allowed in the first hour, 800 ml in

the first two hours or 300 ml/h in the first 3 hours. Over longer periods, the maximum volume of blood loss is 1,000 ml in the first 4 hours or 1,200 ml in the first 5 hours. However, these values are always individualized considering the patient's hemodynamic status, blood volume, other coagulation factors to be corrected and bleeding tendency. Our study showed data quite comparable to the published values for bovine and porcine UFH groups, with volume bleeding within the normal limits described above. Two patients presented bleeding above normal levels. Abnormal bleeding can lead to further surgical intervention. Some risk factors have been identified in need for surgical re-exploration due to bleeding in cardiac surgery with ECC and include advanced age, presence of renal failure, non-coronary surgery, prolonged ECC, and thrombolytic therapy 48 hours before the surgical procedure,[5] among others. The percentage of re-operation observed in the bovine UFH group was 0.98%, well below the published values, ranging from 3 to 5%. In the porcine UFH group, the rate of re-operation was similar to that published (3.08%).[20,21]

The systemic response to heparin may present differences among individuals, with either favorable or adverse effects from its anti-coagulant properties.[22,23] Therefore, monitoring its use and the safety of its effectiveness are fundamental to avoid clot formation during ECC. This study presented two cases of thrombotic complications, one from each treatment group. Published data show that ACT values above 400 seconds are considered safe during ECC.[24,25] Our study showed that the bovine UFH used was effective in the patient's anticoagulation, maintaining ACT levels above 400 seconds for most patients during the whole procedure. Three patients (1.47%) presented ACTs less than 400 seconds after the initial dose of bovine UFH but no clinical report of pro-coagulation changes; correction with a dose of heparin (usually 50 mg) was made to reach the target level. Some patients presented ACT values of over 2,000 seconds, which are considered uncoagulable, but patients did not show any complication. The reasons for the discrepancy between the high ACT value and the lack of bleeding in these cases are not clear from the clinical records.

In their 25-year review of coronary artery bypass grafting surgeries, Sellman et al.,[26] reported a 3.7% rate of bleeding re-operations not related to a specific site, suggesting the presence of blood dyscrasia.[26] However, in our study, both groups seem to respond similarly in clinical terms; the procedure was safe and reached baseline ACT levels after protamine administration without any adverse medical event. A few patients (23.5% of bovine UFH and 35.4% of porcine UFH) needed an additional dose of protamine. The reversibility of heparin by protamine is usually observed with a protamine dose of about 75 to 120% of the bovine heparin dose administered, while porcine UFH requires a higher dose of protamine for its neutralization.[27] Gomes et al.,[28] found no statistically significant difference between bovine and porcine heparin regarding the dosage used, ACT, total bleeding after surgery and protamine dosage needed for neutralization.[28]

Performing surgical studies as clinical randomized trials is challenging.[29,30] Observational studies serve to fill the gap by evaluating real-life situations, thus being closer to external validity. Our research has the limitation of being descriptive only, because of its exploratory and retrospective nature, where patients were submitted to surgery in different years, by different teams and following non-standard procedures. However, we were not looking for comparative results at this point. Rather, we aimed to report the use of bovine UFH in routine medical practice. This preliminary analysis of safety supports larger, comparable studies.

Conclusion

In conclusion, this study contributes to more clinical data available concerning the use of bovine UFH. The adverse events reported were expected according to the nature of the drug, and bovine UFH was safe for on-pump cardiac surgery.

Acknowledgment

The authors acknowledge comprehensive editorial and writing assistance from Mariana Matos M.D., medical writer.

The research team presented part of the study results as a poster in the 45th Brazilian Congress of Cardiovascular Surgery in 2018.

Author contributions

Conception and design of the research: Torres FAL, Torres ACB, Cordeiro TMG. Acquisition of data: Torres FAL, Torres ACB, Ribeiro A, Maia CO, Almeida FP, Roceto J, Matkovski JA, Kovalski MG, Pizato VA. Analysis and interpretation of the data: Torres FAL,

Torres ACB, Cordeiro TMG. Statistical analysis: Torres FAL. Obtaining financing: Torres FAL. Writing of the manuscript: Torres FAL, Torres ACB, Cordeiro TMG. Critical revision of the manuscript for intellectual content: Torres FAL, Cordeiro TMG.

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 Sant´Ana* – Ponta Grossa, PR under the protocol number 1844221/2016. 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. Torrati F, Dantas R. Extracorporeal circulation and complications during the immediate postoperative period for cardiac surgery. Acta Paul Enferm. 2012;25(3):340-5.
2. Dobrovolskaia MA, McNeil SE. Safe anticoagulation when heart and lungs are "on vacation". Ann Transl Med. 2015;3(S1):S11.
3. Aquino RS, Pereira MS, Vairo BC, Cinelli LP, Santos GR, Fonseca RJ, et al. Heparins from porcine and bovine intestinal mucosa: are they similar drugs? Thromb Haemost. 2010;103(5):1005-15.
4. Fu L, Li G, Yang B, Onishi A, Li L, Sun P, et al. Structural characterization of Pharmaceutical heparins prepared from different animal tissues. J Pharm Sci. 2013;102(5):1447-57.
5. Junqueira DR, Viana TG, Peixoto ER, Barros FC, Carvalho Md, Perini E. Heparin pharmacovigilance in Brazil. Rev Assoc Med Bras. 2011; 57(3):322-26.
6. Santos GR, Tovar AM, Capillé NV, Pereira MS, Pomin VH, Mourão PA. Structural and functional analyses of bovine and porcine intestinal heparins confirm they are different drugs. Drug Discov Today. 2014;19(11):1801-7.
7. FDA. Food and Drug Administration. Proposal to Encourage the Reintroduction of Bovine Heparin to the US Market. [Acessed in 25 Nov 2015]. Available from: http://www.fda.gov/advisorycommittees/committeesmeetingmaterials/scienceboardtothefoodanddrugadministration/ucm399395.htm
8. Blossom DB, Kallen AJ, Patel PR, Elward A, Robinson L, Gao G, et al. Outbreak of Adverse Reactions Associated with Contaminated Heparin. N Engl J Med. 2008;359(25):1-15.
9. Francis JL, Palmer GJ, Moroose R, Drexler A. Comparison of bovine and porcine heparin in heparin antibody formation after cardiac surgery. Ann Thorac Surg. 2003;75(1):17-22.
10. Tovar AM, Teixeira LA, Rembold SM, Leite M Jr, Lugon JR, Mourão PA. Bovine and porcine heparins: different drugs with similar effects on human hemodialysis. BMC Res Notes. 2013 Jun;6:230.
11. Mulloy B, Gray E, Barrowcliffe TW. Characterization of unfractionated heparin: comparison of materials from the last 50 years. Thromb Haemost. 2000;84(6):1052-6.
12. Glauser BF, Santos GRC, Silva JD, Tovar AMF, Pereira MS, Vilanova E, et al. Chemical and pharmacological aspects of neutralization of heparins from different animal sources by protamine. J Thromb Haemost. 2018;16(9):1789-99.
13. Barroso RC, Mendonça JT, Carvalho MR, Costa RK, Santos JE. Avaliação da protamina na neutralização da heparina após circulação extracorpórea. Rev Bras Cir Cardivasc. 2001;17(1):54-60.
14. Lopes CT, Brunori EF, Cavalcante AM, Moorhead SA, Swanson E, Lopes Jde L, et al. Factors associated with excessive bleeding after cardiac surgery: A prospective cohort study. Heart Lung. 2016;45(1):64-9.e2.
15. Fathi M. Heparin-induced thrombocytopenia (HIT): Identification and treatment pathways. Glob Cardiol Sci Pract. 2018;2018(2):15.
16. Woodman R, Harker L. Bleeding complications associated with cardiopulmonary bypass. Blood. 1990;76(9):1680-97.
17. Rezende E, Morais G, Silva Junior JM, Oliveira AM, Souza JM, Toledo DO, et al. Thrombocytopenia in cardiac surgery: diagnostic and prognostic importance. Rev Bras Cir Cardiovasc. 2001;26(1):47-53.
18. Cuker A. Clinical and Laboratory Diagnosis of Heparin-Induced Thrombocytopenia: An Integrated Approach. Semin Thromb Hemost. 2014;40(1):106-14.
19. Salis S, Mazzanti VV, Merli G, Salvi L, Tedesco CC, Veglia F, et al. Cardiopulmonary bypass duration is an independent predictor of morbidity and mortality after cardiac surgery. J Cardiothorac Vasc Anesth. 2008;22(6):814-22.
20. Miana LA, Atik FA, Moreira LF, Hueb AC, Jatene FB, Auler Jr JO, et al. Risk factors for postoperative bleeding after adult cardiac surgery. Braz J Cardiovasc Surg. 2004;19(3):280-86.
21. Kouchoukos NT, Blackstone EH, Doty DB, Hanley FL, Karp RB. Hypothermia, circulatory arrest and cardiopulmonary bypass. In: Kirklin/Barratt-Boyes Cardiac Surgery: Morphology, Diagnostic Criteria, Natural History, Techniques, Results and Indications, ed. Karp Elsevier Science, 3rd ed. PA: Churchill Livingstone; 2003:p.67-132.
22. Baugham DR, Woodward PM. A collaborative study of heparin from different sources. Bull Wid Hith Org.1970; 42(1):129-49.
23. Fiser WP, Read RC, Wright FE, Vecchio TJ. A randomized study of beef lung and pork mucosal heparin in cardiac surgery. Ann Thorac Surg. 1983;35(6):615-20.
24. Effeney DJ, Goldstone J, Chin D, Krupski WC, Ellis RJ. Intraoperative anticoagulation in cardiovascular surgery. Surgery. 1981;90(6):1068-74.
25. Sklehan TM, Heflin DW. Optimal ACT sampling interval in pediatric and adult patients after systemic heparinization. Anesthesiology. 1989;71(Suppl 3A):289.

26. Sellman M, Intonti MA, Ivert T. Reoperations for bleeding after coronary artery bypass procedures during 25 years. Eur J Cardiothorac Surg. 1997;11(3):521-7.

27. Frater RW, Oka Y, Hong Y, Tsubo T, Loubser PG, Masone R. Protamine-induced circulatory changes. J Thorac Cardiovasc Surg. 1984;87(5):687-92.

28. Gomes WJ, Leal JC, Braile DM, Guimarães JA, Lopes RD, Lima MA, et al. A Brazilian perspective for the use of bovine heparin in open heart surgery. Int J Cardiol. 2016 Nov 15;223:611-2.

29. Wu R, Glen P, Ramsay T, Martel G. Reporting quality of statistical methods in surgical observational studies: protocol for systematic review. Syst Rev. 2014 Jun;3:70.

30. Demange MK, Fregni F. Limits to clinical trials in surgical areas. Clinics. 2011;66(1):159-61.

International Journal of Cardiovascular Sciences. 2020; 33(3):243-244

EDITORIAL

Is Bovine Heparin, an Old Fellow, a Safe Anticoagulation Approach during Extracorporeal Circulation Inside the Cardiac Operating Room?

Ivis Levy Fernandes Martins and Christianne Bretas Vieira Scaramello

Universidade Federal Fluminense, Niterói, RJ – Brazil

Antithrombotic agents include anticoagulants, antiplatelet and fibrinolytic drugs. They are prescribed in several situations related to hemostasis disturbances that favor thrombi formation. Since bleeding is a common adverse effect of these drugs, a cost-benefit analysis of antithrombotic therapy prior to surgery should be performed.[1] In order to consider the preoperative therapy for patients undergoing cardiac surgery, the risk of thrombosis must outweigh the risk of bleeding. Nonetheless, the literature has reported the use of anticoagulant therapy with unfractionated heparin (UFH) during extracorporeal circulation (ECC) inside and outside the cardiac operating room.[1-4]

The development of the heart-lung machine made ECC possible. Therefore, heart surgery became a routine practice. The literature describes that complications related to ECC have diminished due to modern monitoring, highly trained staff, special cannulation methods, as well as the latest advances in techniques.[2] However, some authors suggest that guidelines based on more researches would improve the safety of this procedure.[3] During cardiac surgery, ECC preserves the functional characteristics of the heart, provides a clean surgical environment and offers safety to the team.[4]

Heparin is a sulfated polysaccharide. It was the first anticoagulant drug approved and is one of the oldest in clinical use, being the second most widely used pharmaceutical drug by mass. Glycosaminoglycan heparin is a natural compound processed to pharmaceutical grade heparin, which can undergo controlled depolymerization to produce low-molecular-weight heparins (LMWHs), whose molecular weights are approximately one-third that of the parent heparin. UFH binds with high affinity to antithrombin, increasing its ability to inhibit both factor Xa and thrombin in the coagulation cascade, whilst LMWHs primarily inhibit factor Xa, and are used therapeutically because of their improved pharmacokinetics and reduced side effects over UFH.[5,6]

UFH has also been manufactured from different mammalian sources, such as porcine (pig), bovine (cow) and ovine (sheep) tissues. Nowadays, there are some concerns about a shortage of porcine heparin. Thus, regulatory agencies are currently considering the introduction of bovine UFH for parenteral indications, and ovine heparin is being developed in non-US markets.[6] For this reason, recent studies have discussed the use of bovine UFH in cardiac surgery.[7,8]

The paper published by Torres et al.,[7] in the International Journal of Cardiovascular Sciences, reports the safety of bovine UFH evaluated during cardiac pump surgery. The study included a retrospective and descriptive analysis. The authors analyzed the medical records of all patients undergoing cardiac surgery with ECC using bovine UFH (supplied by Eurofarma Laboratories S.A.), between October 2008 and November 2012, and porcine UFH (supplied by Cristália and Blausiegel Laboratories), between June 2013 and December 2014, at the Heart Surgery Institute of Hospital Bom Jesus in Ponta Grossa (Paraná, Brazil). Patients were excluded from the study if they had received UFH, LMWH, oral anticoagulants and/or fibrinolytics before the procedure. They were also excluded in case of absence of preoperative platelet count and/or cardiac surgery performed in the presence of severe sepsis, with high risk of widespread intravascular coagulation. Pre- and postoperative

Keywords

Heparin; Blood Coagulation; Extracorporeal Circulation; Cardiac Surgical Prcedures; Patient Safety.

Mailing Address: Christianne Bretas Vieira Scaramello
Rua Prof. Hernani Mello, 101. Postal Code: 24210-130, Niterói, RJ – Brazil.
E-mail: chrisbretas@gmail.com

DOI: https://doi.org/10.36660/ijcs.20200077

data were also collected. The study outcomes were: bleeding, thrombocytopenia, postoperative vasoplegia, activated clotting time shorter than 400 seconds and coagulation phenomena, such as blood clotting with bovine UFH (data on porcine UFH were also collected only as exploratory means).

Torres et al.,[7] evaluated 204 medical records of eligible patients who used bovine UFH. Out of these patients, 66.18% presented thrombocytopenia, whereas 1.04% presented bleeding of more than 2000 mL, within the first 24 hours of the postoperative period. Only one patient presented clots in the surgical field. Median activated clotting time increased five-fold after the first dose of heparin and, after protamine, it returned to similar baseline values. Based on these findings, the authors have concluded that bovine UFH does not present unusual adverse effects and can be considered safe for on-pump cardiac surgery.

Gomes et al.,[8] have also published a paper on a preliminary study evaluating the safety and important clinical aspects of bovine UFH use in heart surgery and compared it to porcine heparin, both obtained from intestinal mucosa. Data were extracted from medical records as well. The main finding of this work was in accordance to Torres et al[7], as similar data were obtained from bovine and porcine UFH treated patients. They have evaluated bleeding volume, modulation of clotting, presence of clot in the surgical field during ECC, activated partial thromboplastin time and specific anti-Xa anticoagulant activity. The authors concluded that bovine UFH may be the solution for the tainted heparin supply.

Although the paper presented by Torres et al.,[7] has limitations consistent with retrospective studies, it is an important contribution to the field. The use of bovine UFH is on the rise due to contamination of porcine UFH with oversulfated chondroitin sulfate, which has caused serious adverse effects. Therefore, studies that corroborate the safety of bovine UFH are welcome.

References

1. Kreuziger LB, Karkouti K, Tweddel J, Massicotte MP. Antithrombotic therapy management of adult and pediatric cardiac surgery patients. J Thromb Haemost. 2018;16(11):2133-46.
2. Feindt P, Benk C, Boeken U, Bauer A, Mehlhorn U, Gehron J, et al. Use of extracorporeal circulation (ECC) outside the cardiac operating room: indications, requirements and recommendations for routine practice. Thorac Cardiovasc Surg. 2011;59(2):66-8.
3. Lukaszewski M, Kosiorowska K, Kościelska-Kasprzak K, Jakubaszko J, Bielicki G, Jasiński M. The use of modern monitoring techniques and methodologies in conducting extracorporeal circulation: a place for Quantum Heart Lung Machine. Kardiol Pol. 2019;77(6):642-4.
4. Torrati FG, Dantas RAS. Extracorporeal circulation and complications during the immediate postoperative period for cardiac surgery. Acta Paul Enferm. 2012; 25(3):340-5.
5. Devlin A, Mycroft-West C, Procter P, Cooper L, Guimond S, Lima M, et al. Tools for the quality control of pharmaceutical heparin. Medicina. 2019; 55(10):1-19.
6. Kouta A, Jeske W, Hoppensteadt D, Iqbal O, Yao Y, Fareed J. Comparative pharmacological profiles of various bovine, ovine, and porcine heparins. Clin Appl Thromb Haemost. 2019;25:1-9.
7. Torres FAL, Torres ACB, Ribeiro A, Maia CO, Almeida FP, Roceto J, et al. A Retrospective Study on Unfractionated Bovine Heparin Safety in On-Pump Cardiac Surgery. Int J Cardiovasc Sci. 2020; 33(3):235-242.
8. Gomes WJ, Leal JC, Braile DM, Guimarães JA, Lopes RD, Lima MA, et al. A Brazilian perspective for the use of bovine heparin in open heart surgery. Int J Cardiol. 2016;15(223):611-2.

International Journal of Cardiovascular Sciences. 2020; 33(3):245-251

ORIGINAL ARTICLE

Association between Central Obesity and Biochemical Markers of Cardiometabolic Risk in Elderly Attended in Geriatric Ambulatory – Lagarto/SE

Ana Caroline de Souza Almeida,[2] Carolina Cunha de Oliveira,[1] Emanuelle Dias Costa,[2] Adenilda Queiroz S. Deiró[2]

Universidade Federal de Sergipe,[1] Sergipe, SE – Brazil
Universidade Federal da Bahia,[2] Salvador, BA – Brazil

Abstract

Backgroud: Central obesity, especially visceral adipose tissue (VAT), represents a health risk due to its endocrine and metabolic capacity, contributing to the development of the atherogenic profile and strongly associating with cardiovascular morbimortality.

Objective: To identify the association between central obesity and biochemical markers of cardiometabolic risk in elderly patients treated at a geriatric outpatient clinic in Lagarto-SE.

Method: This is a cross-sectional study of 159 elderly people of both sexes. Central adiposity was considered an independent variable, identified by measuring the Waist Circumference (WC). Total Cholesterol (TC), LDL-c, HDL-c, non-HDL-c, triglycerides, glycemia and Castelli I and II indices were considered dependent variables. Pearson's chi-square test was used to evaluate the association between central obesity and biochemical markers of cardiometabolic risk. Those with $p < 0.20$ were used in the bivariate regression analysis, adopting a 95% confidence interval.

Results: Mean age was 70.9 ± 7.5 years. Central obesity was present in 43.2% of males and 56.8% of females ($p = 0.002$). There was statistically significant association between HDL-c, HDL-C and Castelli I Index and central obesity. Individuals with central obesity are 2.48 and 3.13 times more likely to develop changes in HDL-C and Castelli I index, respectively.

Conclusion: There is an association between central obesity and biochemical markers of cardiometabolic risk in the elderly. (Int J Cardiovasc Sci. 2020; 33(3):245-251)

Keywords: Cardiovascular Diseases; Obesity; Metabolic Syndrome; Hypertension; Diabetes Mellitus; Risk Factors; Prevention and Control; Dyslipidemias; Life Style; Elderly.

Introduction

Cardiometabolic risk factors (RF) have been widely studied nowadays, with special focus on central obesity, excessive weight, dyslipidemia, Systemic Arterial Hypertension (SAH), insulin resistance and Diabetes Mellitus (DM).[1-4] Central obesity, especially visceral adipose tissue (VAT), represents a health risk due to its metabolic and endocrine capacity, contributing to the development of an atherogenic profile, in addition to being strongly associated with cardiovascular morbidity and mortality.[5,6]

Roriz et al.,[7] highlight that metabolic changes that promote the onset of chronic diseases are more related with visceral adipose tissue than with excessive weight, and that these conditions increase the need for drug treatment and interfere in the quality of life of individuals.

Mailing Address: Carolina Cunha de Oliveira
Fundação Universidade Federal de Sergipe - Departamento de Nutrição - Avenida Governador Marcelo Déda, 13. Postal Code: 49400-000, Centro, Lagarto Sergipe, SE - Brazil
E-mail: carol_cunh@yahoo.com.br

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

Manuscript received on February 25, 2019; reviewed on May 26,2019; accepted on July 30,2019.

The individuals with high VAT levels tend to have insulin resistance, hyperglycemia, hypertriglyceridemia, increased low density lipoprotein (LDL) serum levels and reduced high density lipoprotein (HDL-C) concentration.[8] HDL-C reduction in viscerally obese patients represents the main factor responsible for increased total cholesterol/HDL-C ratio, and this relationship is a strong risk predictor for cardiovascular disease.[5,6,9]

According to Piepoli et al.,[10] age is the main cardiovascular risk factor and most individuals aged 65 years are already considered at high risk. Thus, it is of major relevance to determine the associations of metabolic RF with advanced age, especially among the population in the northeast of Brazil, where there are no studies in this context, due to its negative influence on functional capacity, as well as to the costs incurred to the Brazilian Unified Health System (SUS) for its treatment.[11-14]

The objective of this study is to determine the association between central obesity and biochemical markers of cardiometabolic risk in elderly patients treated at a geriatric outpatient clinic in the city of Lagarto-SE.

Materials and Methods

This is a cross-sectional, primary data collection study, composed by a sample selected by convenience of 159 elderly individuals (aged ≥ 60 years), of both sexes, treated at a geriatric outpatient clinic in the city of Lagarto-SE.

The inclusion criteria used in the research were: patients aged ≥ 60 years, registered at the reference outpatient service and who accepted to participate voluntarily. The exclusion criteria were: patients with abdominal injury or tumors, hepatomegaly and/or splenomegaly, ascites and those who had undergone abdominal surgery recently which could compromise the verification of abdominal fat measures.

The data were collected using a standardized questionnaire, applied by duly trained individuals, following standardized procedures for data collection, such as quality control measures and consistency of information.

The selected covariables were: sex (male and female), age in complete years, self-referred skin color (black; non-black), education (uneducated/Incomplete middle school, complete middle school/Incomplete high school, complete high school or more), occupation (receiving assistance/Organic Law of Social Assistance - LOAS), retired, living on income or pension).

Central adiposity (the accumulation of adipose tissue in the abdominal region) was considered an independent variable, determined by waist circumference (WC) measurement, using an inelastic anthropometric tape (Cescorf, Brazil), in accordance with the measurement techniques proposed by Lohman et al.,[15] and classified according to the International Diabetes Federation (IDF) criteria[16] for South American individuals, when WC ≥ 80 cm and ≥ 90 cm for women and men, respectively.

Total cholesterol (TC), LDL-C, HDL-C, Non HDL-C, Triglycerides (TG), Glucose and Castelli's I and II risk indexes were considered dependent variables, obtained upon request and/or through analysis of data contained in the geriatric medical record, over a period of less than one month from data collection. To perform the classification, the criteria established by the V Brazilian Guidelines on Dyslipidemia and Atherosclerosis Prevention[17] and by the Brazilian Diabetes Society Guidelines[18] were used: TC < 200 mg/dL; LDL-C < 160 mg/dL; HDL-C > 40 mg/dl in men and > 50 mg/dl in women; non-HDL-C < 130 mg/dL, TG < 150 mg/dL and Glucose < 100 mg/dL.

Castelli risk index-I (CRI-I) is calculated as TC/HDLc and Castelli risk index-II (CRI-II), as LDLc/HDLc. TC/HDL-C ratio > 4.7 and LDL-C/HDL-C ratio > 3.1 indicate high metabolic risk.

Statistical Analysis

Statistical software SPSS (version 20.0) was used for statistical analysis. The categorical variables were expressed as percentages and the continuous variables, as mean and standard deviation or median and interquartile interval, according to the distribution pattern. The normality of continuous variables distribution was evaluated using the Kolmogorov-Smirnov test. For parametric and nonparametric variables, the unpaired student's t-test and the Mann-Whitney test were used, respectively, for independent samples. All analyses were performed with the statistical significance level of 5% ($p < 0.05$). Pearson's chi-square test was used to assess the association between central obesity and biochemical markers of cardiometabolic risk. Those with $p < 0.20$ were included in the bivariate logistic regression analysis, adopting a CI of 95%.

Ethical aspects

This study was approved by the Committee of Ethics in Research of the Federal University of Sergipe, under the protocol number 559.936, complying with the Resolution

466/2012 on researches involving human beings of the National Health Council of the Brazilian Ministry of Health. Participation in the study was voluntary, by previous signature or digital impression of the Term of Free and Clarified Consent, after patients had been informed about the objectives of the study and the procedures to which they would be submitted. The study did not involve high risk procedures for the individuals. The institution was notified of cases of elderly patients classified as severely ill, so that the necessary procedures and referrals would be performed.

Results

The sample was characterized as individuals with or without central obesity. Thus, out of the 159 of the elderly assessed, central obesity was present in 43.2% of men and 56.8% of women (p = 0.002), with a higher prevalence among black patients (56.8%), uneducated/incomplete middle school (90.4%), retired (87.9%) and with excessive weight (51.2%) (p < 0.001) (Table 1).

The individuals' mean age was 70.9 ± 7.5 years. When the mean values of biochemical markers were assessed,

Table 1 - Description of elderly patients treated at a geriatric outpatient clinic in the city of Lagarto-SE, stratified by central obesity

Variables	Sample	Central obesity		p
		No	Yes	
	n (%)	n (%)	n (%)	
Sex				
Male	79 (49.7)	25 (73.5)	54 (43.2)	0.002
Female	80 (50.3)	9 (26.5)	71 (56.8)	
Skin color				
Black	96 (60.4)	25 (73.5)	71 (56.8)	0.077
Non-black	63 (39.6)	9 (26.5)	54 (43.2)	
Education				
Uneducated/Incomplete middle school	144 (90.6)	31 (91.2)	113 (90.4)	
Complete middle school/incomplete high school	6 (3.8)	0 (0.0)	6 (4.8)	0.301
Complete high school or more	9 (5.7)	3 (8.8)	6 (4.8)	
Current occupation				
Receiving assistance/LOAS	4 (2.5)	1 (2.9)	3 (2.4)	
Retired	140 (88.1)	31 (91.2)	109 (87.9)	
Living on income or pension	4 (2.5)	0 (0.0)	4 (3.2)	0.773
Others	8 (5.0)	1 (2.9)	7 (5.6)	
Unknown	3 (1.9)	1 (2.9)	2 (1.6)	
Nutritional state				
Low weight	37 (23.3)	21 (61.8)	16 (12.8)	
Adequate	57 (35.8)	12 (35.3)	45 (36.0)	< 0.001
Overweight	65 (40.9)	1 (2.9)	64 (51.2)	

LOAS: Organic Law of Social Assistance.

no statistical significance was observed for individuals with or without central obesity (Table 2).

A significant statistical association was observed between the HDL-C (p = 0.019), Castelli's index I (p = 0.040) and central obesity among the elderly (Table 3). These and the non-HDL-C were included in the logistic regression model (Table 4), which showed a positive association between central obesity and low HDL-C (OR = 2.48; CI 95%: 1.15-5.37) and increased TC/HDL-C ratio (OR = 3.13; CI 95%: 1.01-9.76).

Discussion

The association between central obesity and biochemical changes has been widely discussed nowadays[19-21], since visceral fat produces adipocytes which, in turn, are directly linked with inflammatory processes and cardiometabolic complications .[22]

In this sense, this study contributes with the scientific literature because it shows a positive correlation between central obesity and the biochemical markers HDL-C and Castelli's index I. A similar association was observed by several authors[22-24] who identified a positive correlation between WC and the lipid variables: TC, LDL-C, Non-HDL-C and TG. Roriz et al.,[7] also observed an association between the visceral adipose tissue (VAT) area and Glucose, TG and uric acid. However, the biochemicals TC, LDL-C, HDL-C and VLDL-C did not present results with statistical significance.

Castelli's index I was adopted in this study because it is considered a major risk predictor for cardiovascular disease,[5,9] since HDL-C concentrations are inversely proportional to the incidence of atherosclerosis, due to its essential role in protecting the vascular bed, through cholesterol reverse transport.[25] In this process, the HDL-C removes the oxidized lipids of LDL, inhibits the fixation of adhesion molecules and monocytes to the endothelium and stimulates the liberation of nitric oxide.[26] In this context, the data presented are in line with the authors mentioned before, since in the logistic regression analysis we observed that the individuals with central obesity were 2.48 (p = 0.021) and 3.13 (p = 0.049) times more likely to develop changes in HDL-C and Castelli's I index, respectively. Similarly, Cabral et al.,[27] when assessing the association between the phenotype hypertriglyceridemic-waist (HTW) and the cardiometabolic risk in women, also observed a prevalence ratio (PR) of 3.41 (CI 95%: 2.42-4.81) for the HDL-C.

These data corroborate the study conducted by Silva et al.,[14] with older patients with type 2 diabetes,

Table 2 - Descriptive analysis of the variables "age" and "biochemical markers of cardiometabolic risk", stratified by central obesity, in elderly patients treated at a geriatric outpatient clinic in the city of Lagarto-SE

Variables	Sample	Central obesity		p
		No	Yes	
		(n = 34)	(n = 125)	
Age	70.9 (7.5)	70.9 (8.4)	70.9 (7.2)	0.962
TC	192.4 (41.7)	190.7 (51.3)	192.9 (38.9)	0.791
LDL-C[a]	142.0 (119.0-173.0)	141.7 (114.7-174.3)	143.0 (118.0-173.0)	0.993
HDL-C[a]	41.0 (38.0-44.0)	41.0 (37.8-51.0)	40.0 (37.5-43.0)	0.309
Non-HDL-C	150.4 (42.4)	147.3 (51.2)	151.3 (39.8)	0.628
TG[a]	149.0 (137.0-167.0)	141.0 (130.5-162.5)	149.0 (139.0-167.5)	0.114
Glucose[a]	99.0 (91.0-121.0)	98.5 (87.7 -121.0)	101.0 (101.0-125.5)	0.334
Castelli's index I	4.7 (1.3)	4.5 (1.5)	4.8 (1.2)	0.381
Castelli's index II	3.5 (1.1)	3.3 (1.2)	3.5 (1.0)	0.575

Central obesity (WC > 80M; > 90H); High TC (> 200 mg/dL); High LDL-C > 160 mg/dL; Low HDL-C < 40 mg/dL in men and < 50 mg/dL in women, Non-HDL-C < 130 mg/dL, High TG (> 150 mg/dL); High Glucose (> 100 mg/dL); Castelli's index I > 4.7; Castelli's index II >3.1. [a]Data expressed as median (interquartile interval). Other results expressed as mean (standard deviation).

Table 3 - Association between central obesity and biochemical markers of cardiometabolic risk in elderly patients treated at a geriatric outpatient clinic in the city of Lagarto-SE

Clinical variables	Central obesity		p
	No (n = 34)	Yes (n = 125)	
	n (%)	n (%)	
TC			
Adequate	26 (68.4)	76 (62.8)	0.529
Altered	12 (31.6)	45 (37.2)	
LDL-C			
Adequate	26 (68.4)	77 (63.6)	0.590
Altered	12 (31.6)	44 (36.4)	
HDL-C			
Adequate	18 (47.4)	39 (32.2)	0.019
Altered	20 (52.6)	82 (67.8)	
Non-HDL-C			
Adequate	14 (41.2)	36 (28.8)	0.168
Altered	20 (58.8)	89 (71.2)	
TG			
Adequate	23 (60.5)	68 (56.2)	0.638
Altered	15 (39.5)	53 (43.8)	
Glucose			
Adequate	20 (52.6)	62 (51.2)	0.515
Altered	18 (47.4)	59 (48.8)	
Castelli's index I			
Adequate	6 (17.6)	8 (6.4)	0.040
Altered	28 (82.4)	117 (93.6)	
Castelli's index II			
Adequate	17 (50.0)	52 (41.6)	0.381
Altered	17 (50.0)	73 (58.4)	

Table 4 - Logistic regression of biochemical markers of cardiometabolic risk associated with the presence of Central Obesity in elderly patients treated at a geriatric outpatient clinic in the city of Lagarto-SE

Variables	OR (CI 95%)	p
HDL-C		
Adequate	1.00	0.021
Altered	2.48 (1.15-5.37)	
Non-HDL-C		
Adequate	1.00	0.171
Altered	1.73 (0.79-3.79)	
Castelli's index I (TC/HDL-C)		
Adequate	1.00	0.049
Altered	3.13 (1.01-9.76)	

in which 55.6% of men and 76.6% of women (p = 0.024) presented increased cardiovascular risk according with Castelli's index I. However, few studies have used this relationship for predicting the cardimetabolic risk and/or its association with central obesity, which makes it difficult to compare the results with this variable.

The high prevalence of central obesity observed in this study was also seen in 51.9% of the individuals in a study carried out by Pinho et al.,[28] Similar results were presented by Ding et al.,[1] in a multicentric study performed with 12,607 Chinese adults. It is worth mentioning that, although this is applicable to both sexes, these results are more often found in women.[4,24] Corroborating this statement, in a study performed by Soar,[4] the prevalence of abdominal adiposity was statistically higher in older women (76.16%) (p = 0.00). These data agree with those of Cabral,[27] in whose study 67.4% of women also presented high WC. In a study carried out only with elderly patients, Souza[29] observed that the majority of them (91.2%) also had central obesity.

This heterogeneity of abdominal fat distribution between the sexes may be due to the higher body-fat percentage in women as a result of hormonal differences, pregnancy, menopause and the climacteric period.[30]

Therefore, it is worth highlighting the importance of promoting healthy eating habits and lifestyle to reduce cardiometabolic risk factors in the population and, consequently, reduce hospitalization and mortality rates. As evidenced in a study developed in Canada, which assessed the association between adopting healthier lifestyle and decreased cardiovascular RF, for each increase of one healthy lifestyle habit, WC decreased by 4.0 cm and 4.8 cm for men and women, respectively. A decrease in TC of 0.2 mmol/L, in non-HDL-C of 0.2 mmol/L and in TG of 0.1 mmol/L was also observed.[31]

Piepoli et al.,[10] contributing to these data, highlight that, in the last three decades, more than half of the

decline in CVD mortality was attributed to changes in risk factor levels in the population, especially reduction in cholesterol levels, blood pressure and smoking.

The results of this study are added to others, thus aggregating scientific evidence of correlation between central obesity and changes in the biochemical markers of metabolic risk of older patients, which reinforces the adoption of WC measurements in clinical practice and in epidemiologic studies, due to its ease of application, practicality, accuracy and low cost. However, these results should be carefully analyzed, since this study used a cross-sectional design, which does not allow for causal inferences to be made. Besides, the biochemical data may have been affected by medication taken by the patients. Hence, more robust cohort studies are required to further investigate these parameters, including lifestyle, smoking and blood pressure assessments, as recommended by the European Society of Cardiology and other Societies on Cardiovascular Disease Prevention in Clinical Practice.[10]

Conclusion

We conclude that there was an association between central obesity and biochemical markers of cardiometabolic risk in the elderly patients who participated in the study. The findings suggest the need for better monitoring of these markers, as well as of VAT accumulation, even considering the use of more accurate measurement techniques, such as computed tomography and magnetic resonance, so that adequate health strategies can be provided in order to reduce the number of hospitalizations and deaths by these causes.

Author contributions

Conception and design of the research: Oliveira CC, Costa ED. Acquisition of data: Costa ED. Analysis and interpretation of the data: Almeida ACS, Oliveira CC, Deiró AQS. Statistical analysis: Oliveira CC. Obtaining financing: Oliveira CC. Writing of the manuscript: Almeida ACS. Critical revision of the manuscript for intellectual content: Almeida ACS, Oliveira CC, Costa ED, Deiró AQS.

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 residence completing work in Clinical Nutrition submitted by Ana Caroline de Souza Almeida, from Universidade Federal da Bahia.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Hospital Universitário de Aracajú/Universidade Federal de Sergipe under the protocol number 559.936/2014. 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. Ding L, Xu Y, Wang L, Xu M, Jiang Y, Zhang M, et al. The cardiometabolic risk profile of Chinese adults with diabetes: a nationwide cross-sectional survey. J Diabetes Complications. 2017;31(1):43-52.
2. Maddaloni E, Cavallari I, De Pascalis M, Keenan H, Park K, Manfrini S, et al. Relation of body circumferences to cardiometabolic disease in overweight-obese subjects. Am J Cardiol. 2016;118(6):822-7.
3. Gutiérrez-Repiso C, Soriguer F, Rojo-Martínez G, García-Fuentes E, Valdés S, Goday A, et al. Variable patterns of obesity and cardiometabolic phenotypes and their association with lifestyle factors in the Di@bet.es study. Nutr Metab Cardiovasc Dis. 2014;24(9):947-55.
4. Soar C. Prevalence of cardiovascular risk factors in non-institutionalized elderly. Rev Bras Geriatr Gerontol. 2015;18(2):385-95.
5. Scarsella C, Després JP. Treatment of obesity: the need to target attention on high-risk patients characterized by abdominal obesity. Cad Saude Publica. 2003;19(suppl 1):S7-19.
6. Barroso SG, Abreu VG, Francischetti EA. A participação do tecido adiposo visceral na gênese da hipertensão e doença cardiovascular aterogênica. um conceito emergente. Arq Bras Cardiol. 2002;78(6):618-30.
7. Roriz AKC, Mello AL, Guimarães JF, Santos FC, Medeiros JMB, Sampaio LR. Imaging assessment of visceral adipose tissue area and its correlations with metabolic alterations. Arq Bras Cardiol. 2010;95(6):698-704.
8. Hermsdorff HHM, Monteiro. JBR. Gordura visceral, subcutânea ou intramuscular: onde está o problema? Arq Bras Endocrinol Metab. 2004;48(6):803-11.

9. Castelli WP, Abbott RD, McNamara PM. Summary estimates of cholesterol used to predict coronary heart disease. Circulation. 1983;67(4):730-4.

10. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J. 2016;37(29):2315-81.

11. Dantas CMDHL, Bello FA, Barreto KL, Lima LS. Functional ability of elderly with chronic diseases living in Long-Stay Institutions. Rev Bras Enferm. 2013;66(6):914-20.

12. Ferreira CCC, Peixoto MRG, Barbosa MA, Silveira ÉA. Prevalence of cardiovascular risk factors in elderly individuals treated in the Brazilian Public Health System in Goiânia. Arq Bras Cardiol. 2010;95(5):621-8.

13. Alves LC, Leimann BCQ, Vasconcelos MEL, Carvalho MS, Vasconcelos AGG, Fonseca TCO et al The effect of chronic diseases on functional status of the elderly living in the city of São Paulo, Brazil. Cad. Saúde Pública. 2007;23(8):1924-30.

14. Silva RCP, Simões MJS, Leite AA. Fatores de risco para doenças cardiovasculares em idosos com diabetes mellitus tipo 2. Rev Ciênc Farm Básica Apl. 2007;28(1):113-21.

15. Lohman TG, Roche AF, Martorell R. Anthropometric standardization reference manual. Champaign, IL: Human Kinetics Books; 1988.

16. Alberti KG1, Zimmet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome--a new worldwide definition. Lancet. 2005;366(9491):1059-62.

17. Xavier HT, Izar MCO, Faria Neto JR, Assad MH, Rocha VZ, Sposito AC, et al. V Diretriz Brasileira de Dislipidemias e Prevenção da Aterosclerose. Arq Bras Cardiol. 2013;101(4 supl 1):1–20.

18. Oliveira JEP, Foss-Freitas MC, Montenegro Jr RM, Vencio S. Diretrizes da Sociedade Brasileira de Diabetes 2017-2018; 2017.

19. Bertoni VM, Guattini VLO, Vieira BA, Sauer P, Piovesan CH, Marcadenti A. TG/HDL-c ratio and anthropometric indexes among men and women admitted in a tertiary hospital. Rev Bras Nutr Clin. 2015;30(1):9-14.

20. Oliveira CC De, Roriz AKC, Moreira P de A, Eickemberg M, Amaral MTR, Passos LCS, et al. Anthropometric indicators associated with Hypertriglyceridemia in the Prediction of visceral fat. Rev Bras Cineantropom Desempenho Hum. 2014;16(5):485-93.

21. Silva ARA, Dourado KF, Pereira PB, Lima DSC, Fernandes AO, Andrade AM, et al. TG/HDL-c Ratio and Anthropometric Indicators as Cardiovascular Disease Risk Predictors. Rev Bras Cardiol. 2012;25(1):41-9.

22. Garcez MR, Pereira JL, Fontanelli MM, Marchioni DML, Fisberg RM. Prevalence of dyslipidemia according to the nutritional status in a Representative Sample of São Paulo. Arq Bras Cardiol. 2014;103(6):476-84.

23. Rocha FL, Menezes TN, Melo RLP, Pedraza DF. Correlation between indicators of abdominal obesity and serum lipids in the elderly. Rev Assoc Med Bras. 2013;59(1):48-55.

24. Montenegro Neto AN, Oliveira SSM, Dantas de Medeiros AC, da Silva Portela A, Moreira da Silva Dantas P, Irany Knackfuss M. Estado nutricional alterado e sua associação com perfil lipídico e hábitos de vida em idosos hipertensos. Arch Latinoam Nutr. 2008;58:350-6.

25. Leança CC, Passarelli M, Nakandakare ER, Quintão ECR. HDL: the yin-yang of cardiovascular disease. Arq Bras Endocrinol Metab. 2010;54(9):777-84.

26. Faludi AA, Izar MCO, Saraiva JFK, Chacra APM, Bianco HT, Afiune Neto A, et al. Atualização da diretriz brasileira de dislipidemias e prevenção da aterosclerose - 2017. Arq Bras Cardiol. 2017;109(2 supl 1):1-76.

27. Cabral NAL, Ribeiro VS, Cunha França AKT, Salgado JVL, Santos AM, Salgado Filho N, et al. Cintura hipertrigliceridêmica e risco cardiometabólico em mulheres hipertensas. Rev Assoc Med Bras. 2012;58(5):568-73.

28. Pinho CPS, Diniz A da S, Arruda IKG, Filho MB, Coelho PC, Sequeira LAS, et al. Prevalence of abdominal obesity and associated factors among individuals 25 to 59 years of age in Pernambuco State, Brazil. Cad Saúde Pública. 2013;29(2):83-9.

29. Souza MCM, Nóbrega SS, Tomiya MTO, de Arruda IKG, Diniz A da S, de Lemos MCC. Central adiposity among elderly women in a gerontology-geriatric unit. Rev Bras Geriatr Gerontol. 2016;19(5):787-96.

30. Ronsoni R.M, Coutinho MSSA, Pereira MR, Silva RH, Becker IC. Prevalence of abdominal obesity and associated factors among individuals 25 to 59 years of age in Pernambuco State, Brazil. Cad Saúde Pública. 2013;29(2):313-24.

31. Leroux C, Gingras V, Desjardins K, Brazeau AS, Ott-Braschi S, Strychar I, et al. In adult patients with type 1 diabetes healthy lifestyle associates with a better cardiometabolic profile. Nutr Metab Cardiovasc Dis. 2015;25(5):444-51.

EDITORIAL

Metabolic Syndrome

Elizabete Viana de Freitas and Kalil Lays Mohallem

Hospital Pró-cardíaco, Rio de Janeiro, RJ - Brazil

Introduction

Metabolic Syndrome (MS) is a complex disorder characterized by a group of Risk Factors (RF), including changes in glycemic levels, insulin resistance, lipid profile, blood pressure levels and central obesity (visceral adipose tissue – VAT), which increase the incidence of cardiovascular diseases often associated with ageing. [1]

It is estimated to affect over 20% of the global adult population, and women are at greater risk. Central (visceral) obesity is thought to be the predominant RF for MS, especially among overweight and low-educated elderly.[2]

Central obesity can be called an underlying risk factor for cardiovascular disease (ASCVD). It is called this because it raises the risk for ASCVD through other RFs, including major RFs (hypercholesterolemia, hypertension, hyperglycemia) and emerging RFs (atherogenic dyslipidemia, insulin resistance, proinflammatory state, prothrombotic state). The constellation of major and emerging RFs that make up the MS can be called metabolic RFs and, since predictions estimate that 50% of adults will be classified as obese by 2030, it is likely that MS will be a significant problem for health services and a drain on health economies.[3]

Abdominal obesity does not always occur in individuals with elevated BMI. It was recognized as early as 1981 that normal weight, metabolically obese individuals existed due to the presence of excessive visceral fat deposits.[4]

Keywords

Metabolic Syndrome; Risk Factors; Prevention and Control; Obesity; Dyslipidemias; Hypertension; Diabetes Mellitus, Elderly.

In this issue of IJCS, Almerida et al., [5] present a study with 159 patients from Lagarto/Sergipe, whose mean age was 70.9± 7.5 years. Central obesity was present in 43.2% of men and 56.89% of women and was associated with changes in HDL-C levels. The study adds to the understanding of this condition in a Brazilian region where few studies of this kind have been carried out and confirms its high prevalence.

It is important to highlight that measuring waist circumference in older adults can be difficult due to the curvature of the spine and vertebrae and walking or standing limitations. It may be necessary to adjust the cutoff for waist circumference based on age and ethnicity. Sex-specific cut-off criteria for the general population are ≥102 cm (40 in) for men and ≥ 88 for women (35 in).[1] See Table 1.

When the BMI is used as a measure of obesity, only a modest association with cardiovascular RFs is found.

Table 1 – ATP III Clinical identification – Three or more risk factors present

Risk Factor	Defining Level
Waist circumference	
Men	≥ 102 cm (>40 in)
Women	≥ 88 cm (325 in)
Triglycerides	≥\ 150 mg/dL
HDL-C	
Men	< 40 mg/dL
Women	< 50 mg/dl
Blood Pressure	≥ 130/≥ 85 mmHG
Fasting Glucose	≥ 110 mg/dL

The American Diabetes Association established a cut point of 100mg/dL

Mailing Address: Elizabete Viana de Freitas
R. Gen. Polidoro, 192. Postal Code: 22280-003, Botafogo, Rio de Janeiro, RJ – Brazil.
E-mail: betevf@gmail.com

DOI: https://doi.org/10.36660/ijcs.20200085

However, when abdominal obesity measurements, such as waist circumference or waist-hip ratio, are included as a measure of abdominal adiposity, a strong association with cardiovascular and metabolic syndrome RFs is found.[6] Therefore, it is important to measure the waist circumference in the patient's routine examination.

Evidence shows that one of the single most important lifestyle changes for the prevention of many chronic diseases is exercise. For this reason, exercise is now recognized as a medical treatment to improve quality of life and functioning in the elderly. There is growing evidence that regular and consistent exercise significantly reduces abdominal fat deposits, *independent of weight loss*.[7]

A systematic review and meta-analysis were conducted by Ostman et al. to determine whether exercise reversed various indices of metabolic syndrome, including body composition, blood cholesterol, fasting blood glucose, fasting insulin, blood pressure and clinical outcome. When the combined exercise group was compared with the control group, the mean difference of: waist circumference was − 3.80 cm (95% CI − 5.65, − 1.95, $p < 0.0001$); systolic blood pressure was − 3.79 mmHg (95% CI − 6.18, − 1.40, $p = 0.002$); and HDL was 0.14 (95% CI 0.04, 0.25, $p = 0.009$). The improvements in waist measurement would suggest that the long-term risks associated with MS were reduced, although the program needs to be tailored to the individual whilst aiming to deliver optimal effects.[8]

Due to population characteristics, further and larger studies are required to improve the diagnosis and treatment of MS in older adults and, consequently, reduce the cardiovascular risk of this growing and vulnerable population.

References

1. Sociedade Brasileira de Cardiologia. Sociedade Brasileira de Endocrinologia e Metabologia. Sociedade Brasileira de Diabetes. Sociedade Brasileira para Estudos da Obesidade. I Diretriz Brasileira de Diagnóstico e Tratamento da Síndrome Metabólica. Arq Bras Cardiol. 2005;84(supl 1):1-28.
2. Park Y-W, Zhu S, Palaniappan L, Heshka S, Carnethon MR, Heymsfield SB. The metabolic syndrome: prevalence and associated risk factor findings in the US population from the third National Health and nutrition examination survey, 1988-1994. Arch Intern Med. 2003;163(4):427–36.
3. Saad MAN, Cardoso GP, Martins WA,Velarde LG, Cruz Filho RA. Prevalence of Metabolic Syndrome in Elderly and Agreement Among Four Diagnostic Criteria. Arq Bras Cardiol. 2014;102(3):263-9.
4. Ruderman NB, Schneider SH, Berchtold P. The "metabolically-obese," normal-weight individual. Am J Clin Nutr. 1981;34(8):1617–21
5. Almeida AC, Oliveira CC, Costa ED, Deiró AQ. Association between Central Obesity and Biochemical Markers of Cardiometabolic Risk in Elderly Attended in Geriatric Ambulatory – Lagarto/SE. Int J Cardiovasc Sci. 2020;33(3):245-251.
6. Brooks GC, Blaha MJ, Blumenthal RS. Relation of C-reactive protein to abdominal adiposity. Am J Cardiol. 2010;106(1):56–61.
7. Davidson LE, Hudson R, Kilpatrick K, Kuk JL, McMillan K, Janiszewski PM, et al. Effects of exercise modality on insulin resistance and functional limitation in older adults: a randomized controlled trial. Arch Intern Med. 2009;169(2):122–31.
8. Ostman C, Smart NA, Morcos D, Duller A, Ridley W, Jewiss D. The effect of exercise training on clinical outcomes in patients with the metabolic syndrome: a systematic review and meta-analysis. Cardiovasc Diabetol 2017;16(1):110.

ORIGINAL ARTICLE

Evaluation of Polymorphisms in IL8 and IL16 Genes in Patients with Acute Coronary Syndrome

Lílian Caroliny Amorim Silva,[1] Romário Martins Araújo,[1] Fábia Carla Silva Soares,[1] Roberto Pereira Werkhauser,[1] Sergio Tavares Montenegro,[2] Tetsuo Tashiro,[3] Viviane do Carmo Vasconcelos Carvalho,[1] Silvia Maria Lucena Montenegro[1]

Instituto Aggeu Magalhães,[1] Recife, PE - Brazil
Real Hospital Português de Beneficência em Pernambuco (RHP),[2] Recife, PE - Brazil
Universidade Federal de Pernambuco (UFPE),[3] Recife, PE - Brazil

Abstract

Background: Acute coronary syndrome (ACS) is a cardiovascular disease caused by obstruction of coronary arteries by atheromatous plaque. Susceptibility to this disease may be related to genetic variations, such as single nucleotide polymorphisms (SNPs).

Objective: In this study, we evaluated the relationship between SNPs in IL8 (rs4073; -251 A/T) and IL16 (rs11556218; T/G) genes and SCA in a Brazilian population.

Materials and Methods: A sample of 200 patients with ACS and 50 non-ACS patients hospitalized at the *Real Hospital Português*, Recife – PE, Brazil, and 220 blood donors (donors) was used. Genotyping was carried out by polymerase chain reaction, and DNA sequencing. Statistical analyzes were performed using the Williams G, Chi-square and Kruskal Wallis tests, using the BioEstat 5.0 program, and the data with a value of $p < 0.05$ were considered significant.

Results: In the IL8 gene, the AT genotype was the most frequent ($p > 0.05$) in all three groups. In the IL16 gene, genotypic distributions were different between patients with ACS and the donor group ($p = 0.002$), with the most frequent G allele in the second group ($p = 0.0052$). The IL-16 cytokine was higher in donors than in patients with ACS ($p = 0.04$) and the G (TG + GG) allele had higher values of this cytokine ($p = 0.01$).

Conclusions: The results demonstrate the important role of the rs11556218 SNP in IL16 gene in SCA, evidencing that the G allele may be associated with a decreased risk of the disease. (Int J Cardiovasc Sci. 2020; 33(3):254-262)

Keywords: Cardiovascular Diseases; Acute Coronary Syndrome; Genotype; Dyslipidemia; Diabetes Mellitus; Obesity; Sedentarism.

Introduction

Acute coronary syndrome (ACS) is a cardiovascular disease (CD) characterized by occlusion of the coronary arteries and most often begins with the rupture of an atherosclerotic plaque in this artery, inducing the formation of a thrombus that occludes partially or totally the vessel.[1] Among the risk factors that influence its development, the presence of diabetes, dyslipidemia, smoking, obesity, sedentarism, hypertension and stress are highlighted. Age, gender and family history are also considered risk factors.[2] In addition, genetic factors may also contribute to a greater susceptibility to disease.[3]

Some genetic polymorphisms have already been linked to the risk of developing CDs in specific populations. Interleukin (IL) -8 is produced by a variety

Mailing Address: Silvia Maria Lucena Montenegro
Instituto Aggeu Magalhães - Av. Professor Moraes Rego, s/n. Postal Code: 50.740-465, Recife, PE - Brazil.
E-mail: silvia@cpqam.fiocruz.br

DOI: https://doi.org/10.36660/ijcs.20181080

Manuscript received on February 08, 2018, revised manuscript on January 22, 2019, accepted on May 13, 2019.

of cell types involved in atherosclerosis, in addition to being expressed in areas rich in macrophages of atherosclerotic lesions.[3-5] In addition to a potential role in the initiation and progression of atherosclerosis, IL-8 can also participate in the complications of this process by acting on destabilization of atherosclerotic plaque and specifically on thrombosis.[3,4] Single nucleotide polymorphism (SNP) in IL8 gene (rs 4073) has been shown to be associated with SCA in different populations. Its frequency is related to a high plasma level of its respective cytokine, which may contribute to an inflammation associated with the infiltration of macrophages and neutrophils, thus providing a substrate for the development of ACS.[5,6] This SNP has the ability to alter the transcriptional activity of the gene, contributing to the increase of IL-8 cytokine levels.[7-9]

IL-16 is a pleiotropic and immunoregulatory proinflammatory cytokine.[10] Elevated levels of this cytokine were detected in patients with CAD.[11] In previous studies, this cytokine is related to the regulation of recruitment and activation of CD4 + T cells in the inflammatory process of CVDs.[12]

Some studies report that the G mutant allele in its gene (rs11556218) is associated with a significantly increased risk of CDs.[13-15] The exact role of IL-16 in the pathogenesis of ACS remains unclear, but it is known that the rs11556218 T/G SNP may influence the expression of IL-16 cytokine and alteration of its serum levels may promote the production of other cytokines IL-1, IL-2 and IL-6 that are involved in the development of ACS.[15]

These findings suggest that SNPs in the IL8 (rs4073) and IL16 (rs11556218) genes may be useful markers of genetic susceptibility to ACS, allowing the identification of high-risk individuals by selecting for more invasive therapies[16] and closer monitoring.

The lack of uniformity in positive results in several populations is the major problem for the study of genetic association.[17] Thus, it is necessary to study SNPs in specific populations to identify their association with diseases in a region.

The aim of this study was to evaluate the association between SNPs in the IL8 (rs4073) and IL16 genes (rs11556218) and the risk of developing ACS. In addition it was our intention to compare our blood donor population with other healthy populations from different countries, to contribute to the identification of molecular markers in disease susceptibility.

Materials and Methods

Study population

Patients with ACS (n = 200) and non-ACS (n = 50) are adults of both genders admitted to the *Real Hospital Português* (RHP), Recife – PE, Brazil. Patients with ACS have their diagnosis performed by the clinical team and laboratory data suggestive of ischemic myocardial injury. Patients with non ACS were admitted to the RHP with other cardiac disease. For both groups, data were collected about the presence of the main risk factors for coronary artery disease such as diabetes mellitus, systemic arterial hypertension and dyslipidemia.

A group of healthy adults (n = 220) blood donors with negative diagnosis for infectious and parasitic diseases was also selected. The collection period was from May 2012 to August 2016 for all subjects participating in the study.

The sample size was obtained through the convenience selection of the patients.

The present study was approved by the Research Ethics Committee of RHP (CAEE: 03187512.2.0000.5202) and all individuals signed the Informed Consent Term.

It was decided not to perform ethnic correspondence, since previous studies in Brazilian populations have shown that skin color or self-defined ethnic origins are not considered accurate as biomarkers for ancestry in Brazil.[18]

Genotyping

Blood was collected in a tube with Ethylene Diamine Tetraacetic Acid (EDTA) and extracted DNA was amplified by the Polymerase Chain Reaction (PCR) method using specific primers and amplification conditions for each SNP (Table 1). As a negative control, reagents without DNA were used. The fragments were visualized on 1% agarose gel and subjected to DNA sequencing using the ABI 3500xL Genetic Analyzer (Applied Biosystems, USA).

Dosage of inflammatory markers: The cytokines were dosed in the serum through the Human Quantikine ELISA Kit (R&D Systems, Minneapolis, MN), following the manufacturer's guidelines, using the Enzyme Lynked Immunosorbent Assay (ELISA) method.

Statistical analysis

The X2 test was used to verify the Hardy-Weinberg equilibrium. Differences between the genotypic

Table 1 – PCR conditions for the analysis of SNPs in IL8 and IL16 genes

SNP	Primers	Amplification conditions	Fragment size	Reference
IL8 rs4073 (A/T)	F: 5′ CATGATAGCATCTGTAATTAAC 3′ 5′ CTCATCTTTTCATTATGTCAGA 3′	1) 95°C – 5 min 2) 95°C – 1min 3) 57°C – 1 min 4) 72°C – 1 min 5) 72°C – 5 min	348 bp	Andia, et al (2013)[19]
IL16 rs11556218 (G/T)	F: 5' GCTCAGGTTCACAGAGTGTTTCCATA 3′ R: 5' TGTGACAATCACAGCTTGCCTG 3′	1) 94°C – 4 min 2) 94°C – 30 seg 3) 60°C – 30 seg 4) 72°C – 30 seg 5) 72°C – 5 min	171 bp	Wu, et al (2011)[15]

Amplification conditions: 1 and 2: Initial denaturation; 3: Ringing; 4 and 5: Extension. PCR: polymerase chain reaction; SNP: single-nucleotide polymorphism.

frequencies were analyzed by the G Williams test and Odds Ratio (OR) with 95% confidence intervals. The multivariate logistic regression model was used to evaluate the association between genetic polymorphisms and risk factors for ACS. Data were considered statistically significant where $p < 0.05$.

Continuous variables were expressed as means and standard deviation (SD) or medians (cytokine dosages). Categorical variables were expressed in absolute and relative values. Kolmogorov-Smirnov or Shapiro-Wilk tests were used to evaluate normality in the continuous variables. Assuming that the quantitative data did not follow normal distribution, non-parametric tests were applied. Kruskal-Wallis test was used to compare the variation of their concentrations between the groups.

Multivariate analysis was performed using a multivariate logistic regression model to evaluate the association between genetic polymorphisms and risk factors for ACS. In the analysis of all the data was used the program BioEstat 5.0.

Results

The distributions of the genotypic frequencies are in accordance with the Hardy-Weinberg equilibrium.

The mean age found in the groups with ACS, without ACS and blood donors was 62 (± 13.0), 58 (± 18.9) and 48 (± 6.3) years old, respectively. The male gender was the most frequent in the three groups evaluated (76.5%, 58% and 85.4%, respectively).

The majority of patients with ACS and non-ACS were non-smokers (69.5% and 82%, respectively) and non-diabetics (55.5% and 68%, respectively). Hypertensive patients accounted for 80.5% of patients with ACS and dyslipidemia was present in 64% of ACS patients and only 14% of those without ACS.

Results for the rs4073 (IL8) SNP demonstrated a higher frequency of the AT genotype in all groups analyzed.

For SNP rs11556218 (IL16), the most frequent genotype in all 3 groups was TT. In addition, TG genotype showed higher frequency in blood donor individuals (35.5%) compared to ACS patients (21.0%; $p = 0.002$). G allele carriers (TG + GG) were more present in donor subjects (36%) than in patients with ACS (23%) ($p = 0.0052$). When comparing the groups with ACS and without ACS, no difference was found in the genotypic distribution (Table 2).

When genetic polymorphisms were evaluated in relation to the main risk factors for ACS (smoking, diabetes, hypertension and dyslipidemias), the IL8 gene showed no association. The rs11556218 SNP in the IL16 gene showed statistical association when analyzed against risk factors hypertension ($p = 0.002$) and dyslipidemias ($p = 0.01$) (Table 3).

From the results of the genotyping for the polymorphisms and considering the significant association between the SNP rs11556218 in the IL16 gene and SCA, the cytokine IL-16 was dosed. For this, 20 samples from patients with ACS (TT = 9),

Table 2 – Distribution of genotypic frequencies of SNPs in the IL8 and IL16 genes in the three groups

Genotype	ACS (N = 200)		NON-ACS (N = 50)		SCA x NON-ACS	DONORS (N = 220)		ACS x DONORS
	N	%	N	%	p	N	%	p
IL8 (rs4073)								
AA	46	23	8	16	0.46	61	27.8	0.31
AT	99	49.5	29	58		111	50.4	
TT	55	27.5	13	26		48	21.5	
AT+TT	154	77	42	84	0.36	159	72.3	0.31
Alleles								
A	191		45			233		
T	209		55			207		
IL16 (rs11556218)								
TT	154	77	33	66	0.30	141	64	0.0026
TG	42	21	16	32		78	35.5	
GG	4	2	1	2		1	0.5	
TG + GG	46	23	17	34	0.17	79	36	0.0052
Alleles								
G	50		18			80		
T	350		82			283		

N: number of patients; p: Williams-G test; SNP: single-nucleotide polymorphism; ACS: acute coronary syndrome.

(TG = 10), (GG = 1) and 20 samples from donor individuals (TT = 9), (TG = 10) and (GG = 1) were used.

The dosages of IL-16 were similar among the three different genotypes in patients with ACS (Figure 1B).

In the donor individuals, the G (TG + GG) allele had higher serum IL-16 levels (701.9 pg/mL) than those with TT genotype (447.7 pg/mL) (p = 0.001) (Figure 1 A).

The dosage of this cytokine was higher in the donor group (563.0 pg/mL) than in patients with ACS (355.4 pg/mL) (p = 0.04) (Figure 1C).

The genotypic frequencies of blood donors were also compared to other healthy populations (Table 4). The results show that for the IL8 gene there was similarity (p > 0.05) in the genotypic distribution between the present study and other Brazilian populations of Maranhão[20] and São Paulo[21] and the populations of Iran[22] and Greece.[9]

Regarding SNP rs11556218 in the IL16 gene, there was a difference between the genotype frequencies of China[23] and Iran[24] when compared to the present study (p = 0.01 and < 0.0001, respectively).

Discussion

The age presents itself as one of the most important risk factors for ACS.[28] According to Dutra et al.,[29] cardiovascular diseases affect mostly elderly individuals. The mean age found in the present study was 62 years old, corroborating the data obtained by Marino et al.,[30] in a study performed with Brazilian patients with ACS who found a mean age of 63 years old and by Shah et al.,[31] studying Scottish patients with ACS with a mean age of 62 years old.

Table 3 – Analysis of the association of SNPs in the IL8 and IL16 genes with the risk factors for ACS

SNP / risk factors	p	Odds ratio	IC 95%
IL8 (rs4073)			
Smoking	0.39	0.73	0.36 – 1.50
Diabetes	0.92	1.03	0.53 – 2.04
Hypertension	0.49	0.73	0.30 – 1.79
Dyslipidemias	0.31	1.43	0.72 – 2.86
IL16 (rs11556218)			
Smoking	0.94	0.97	0.46 – 2.06
Diabetes	0.22	1.54	0.76 – 3.12
Hypertension	0.002	0.26	0.12 – 0.62
Dyslipidemias	0.01	2.68	1.19 – 6.04

SNP: Single Nucleotide Polymorphism; P: multivariate logistic regression; CI: Confidence Interval.

Besides age, gender is also important in the epidemiology of ACS. According to Maas and Appelman,[32] cardiovascular diseases, where ACS is included, usually manifest later in women than in men, partly because of differences in exposure to risk and hormonal factors.[33,34]

In our study, males accounted for 76.5% of ACS patients. Similar data were obtained by Huang et al.,[15] and Bray et al.,[35] who observed the frequency of 80.4% and 68.0% of male in ACS patients of their studies, respectively.

Smoking, diabetes, hypertension and dyslipidemias are considered important in increasing the risk for ACS, however, most of the patients in the present study were neither smokers nor diabetics in both groups (with or without ACS). These data corroborate the study by Guedes et al.,[36] in which the majority of Brazilian patients with CD were not smokers (93.3%). In a study by Vogiatzi et al.,[5] with Greek patients diagnosed with ACS, the majority was not diabetic (64.3%).

Despite this, diabetes and smoking may not have their importance excluded as risk factors for ACS.

Generally, the majority of patients (with or without ACS) had systemic arterial hypertension. These results corroborate the data obtained from patients with ACS in different countries (Australia, Pakistan, Mexico and Japan) who indicated that the majority of the patients were hypertensive, varying between 56.5% in Japan and 68.0% in the Mexico.[14,35,37,38] For the Ministry of Health, this disease is responsible for at least 25% of the deaths due to ACS.[39]

In the present study it was verified that the majority of patients with ACS are dyslipemic (64.0%), similar data were verified by Feijó et al.,[40] Rodrigues et al.,[41] and Andrade et al.,[42] who studied Brazilian patients with CDs and found that 50.5%, 73.9% and 60.1%, respectively, were dyslipemic.

The data about risks factors reinforce that this disease has a multifactorial character. Thereby the genetic component directly participates in the predisposition to ACS.

Regarding the polymorphism in the IL8 gene (rs4073), we observed a higher frequency of the AT heterozygous genotype in the three groups analyzed. Similarly, in a study by Zhang et al.,[6] a prevalence of AT genotype was 47.4% in patients with ACS and 45.9% in the control group.

For the SNP in the IL16 gene (rs11556218), a difference in heterozygous TG genotype frequencies was observed between the group of patients with ACS and the group of blood donors (p = 0.0026). In addition, carriers of the G mutant allele were more present in blood donors than in patients with ACS, suggesting that this allele may have a protective action in ACS.

Discordant data were found in a study by Chen et al..[8] in which the G allele was more frequent in patients with ACS (84.9%) than in the control group (64.2%). However, the authors point that the lack of success in replicating the positive result in other populations is the main problem for genetic association studies.[8]

When comparing the serum levels of IL-16 cytokine, donor individuals presented higher values than patients with ACS (p = 0.04). In addition, among the blood donors, the G (TG + GG) allele presented higher IL-16 values (p = 0.01). These results corroborate the data obtained by Gronberg et al.,[11,43] where the presence of IL-16 on the carotid plaque is associated with a decreased risk of cardiovascular events in studies performed with a Swedish population. This is due to the stabilization of the atherosclerotic plaques, avoiding the ACS disease.[11,43]

The cytokine IL-16 has been described as a pro-inflammatory cytokine. However, there are few studies supporting its possible anti-inflammatory function, identified by the present study.[11,43]

In addition, one hypothesis for the lack of association found between ACS and non-ACS patients

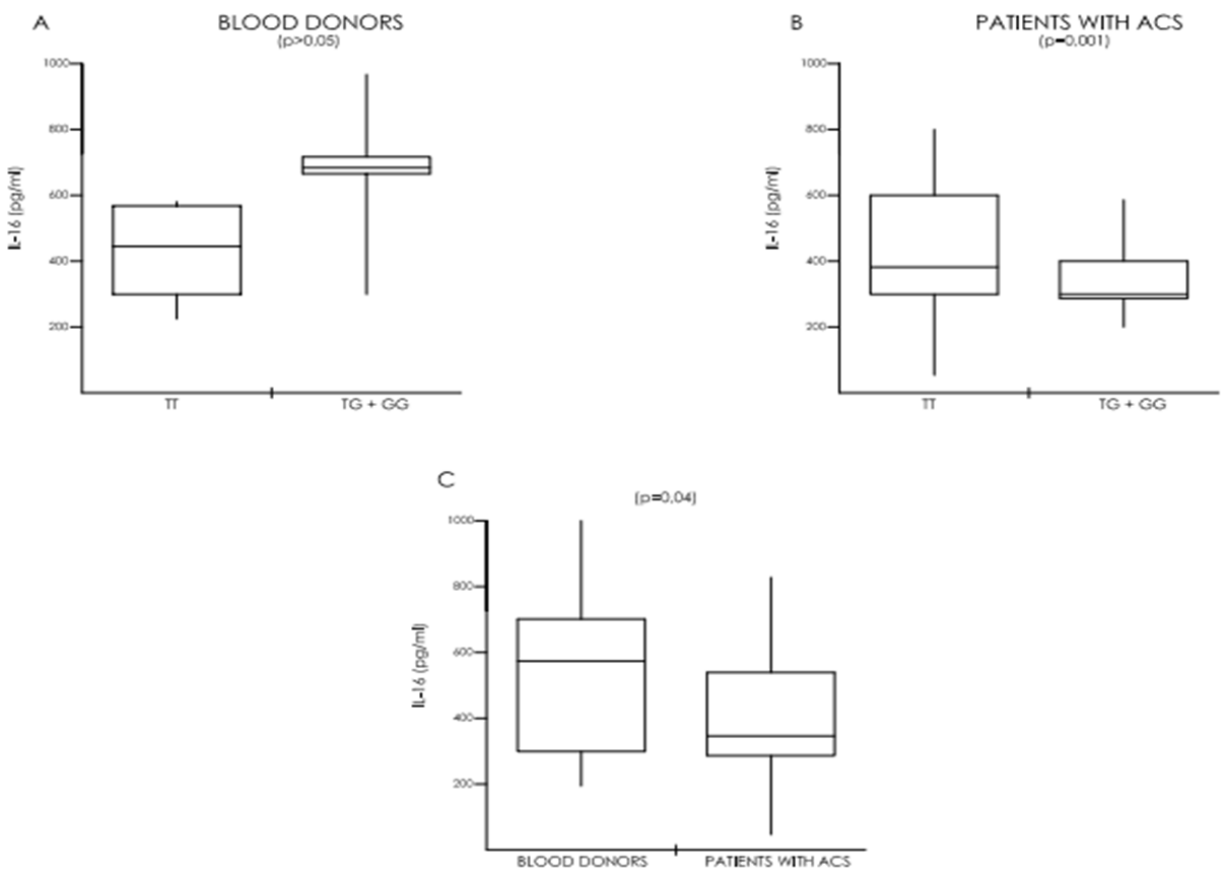

Figure 1 – Box-plot (median and quartiles) of IL-16 dosages in patients with ACS and healthy individuals in different IL16 genotypes. *Box-plot (median and quartiles) of IL-16 dosages in patients with ACS and blood donors in different IL16 genotypes. A) Median IL-16 in blood donors (TT = 447.7 pg/mL; TG + GG = 709.2 pg/mL, p = 0.001); B) Median of IL-16 in patients with ACS (TT = 381.4 pg/ml; TG + GG = 314.9 pg/ml, p = 0.288); C) Median IL-16 in blood donors (563.0 pg/mL) and patients with ACS (355.4 pg/ mL) (p = 0.04); p = Mann-Whitney.*

is that the SNP in the IL16 gene (rs11556218) is involved with CDs in general, not only with ACS, and further studies are needed, with different populations to answer this question.

An association was found regarding the polymorphism in IL16 gene (rs11556218) and the risk factors hypertension and dyslipidemia. These results corroborate the data found by Chen et al.,[7] with 300 patients with ACS who showed a significant association between the homozygous variant (GG) genotype and the hypertension, diabetic and smoker individuals. In addition, the study by Wu et al.,[15] with 326 Chinese patients with ACS also found an association between the GG genotype and the disease in hypertensive, diabetic, smoker, obese and dyslipemic individuals.

The analysis of the frequencies of polymorphisms in genes of medical interest for a disease in a population can become an important tool to understand and evaluate the risks that this disease can bring, as well as its morbidity and mortality. The results can be used in future studies of association between these polymorphisms and different pathologies.

Thus, the present study also evaluated a comparison between the frequencies of polymorphisms in the IL8 and IL16 genes of our healthy, blood donor individuals with several other healthy populations from other countries.

Regarding the IL8 polymorphism, a similarity was observed in the genotypic distribution with two Brazilian populations (Maranhão and São Paulo) and two from other countries (Iran and Greece). With respect to the

Table 4 – Distribution of genotypic frequencies of SNPs in IL8 and IL16 genes in different healthy populations

SNP	Country	N	Genotype frequencies n (%)			p	Reference
			AA	AT	TT		
IL8 (rs4073)	Brazil (Northeast*)	220	61 (27.8)	111 (50.4)	48 (21.5)	1	-
	Brazil (Maranhão)	97	22 (22.7)	46 (47.4)	29 (29.9)	0.28	Frade et al., 2011[20]
	Brazil (São Paulo)	126	38 (30.2)	65 (51.6)	23 (18.2)	0.71	Matos et al., 2011[21]
	Hungary	75	15 (20.0)	30 (40.0)	30 (40.0)	0.01	Farkas Jr et al., 2011[25]
	China	636	80 (12.6)	292 (45.9)	264 (41.5)	< 0.0001	Zhang et al., 2011[6]
	Turkey	38	8 (21.0)	11 (29.0)	19 (50.0)	0.002	Cengiz et al., 2014[26]
	Iran	40	12 (30.0)	17 (42.5)	11 (27.5)	0.62	Khosropanah et al., 2013[22]
	United Kingdom	235	54 (23)	105 (44.7)	76 (32.3)	0.03	Smith et al., 2004[27]
	Greece	126	38 (30.2)	65 (51.6)	23 (18.2)	0.71	Georgitsi et al., 2016[9]
			TT	TG	GG		
IL16 (rs11556218)	Brazil (Northeast*)	220	141 (64.0)	78 (35.5)	1 (0.5)	1	
	China	402	235 (58.4)	151 (37.6)	16 (4.0)	0.01	Tang et al., 2016[23]
	Iran	144	81 (56.3)	48 (33.3)	15 (10.4)	< 0.0001	Azimzadeh et al, 2016[28]

*N: number of individuals; * Present study; p: p-value (G of Williams)*

Brazilian populations, it can be interpreted that despite the intense miscegenation in the country, the genetic characteristics in relation to the SNP evaluated, have been conserved in these populations.

Regarding the SNP in the IL16 gene, no similarities were found when comparing the frequencies of our study with other populations.

The genotypic variety found in the comparison between the results of the present study and other countries leaves us the important observation that further population studies should be carried out in order to understand these similarities or differences found.

Conclusions

The mutant G allele of rs11556218 polymorphism in the IL-16 gene presents a possible protective action in relation to the development of ACS in the studied population.

Regarding the SNP rs4073 (IL8), no association was found with SCA.

The comparison between the frequency of the SNPs rs4073 (IL8) and rs11556218 (IL16) of the present study and other world populations demonstrated a wide genetic variety.

Study limitations

The main limitation of the study refers to the composition of the HEMOPE donor group, since it was not possible to match the ages between this group and the patients. Through literature search, it was possible to observe that the use of blood donors to compose a group of comparisons in genetic studies is adequate, since this group of individuals represents a healthy population in general.

Although it is known that the age for donation ranges from 16 to 69 years, and therefore the age of patients with ACS would be within this age group, during the collection of samples it was observed that the age obtained from the group of was less than 62 years. This fact generated a selection bias.

Therefore, the HEMOPE donor group was used only for comparison of the genotypic and allelic frequencies using the Williams G test and not to establish the odds ratios for the development of ACS.

Acknowledgements

The authors thank the core-facilities laboratories of Institute Aggeu Magalhães, *Fundação Oswaldo Cruz* (Fiocruz - PE) for the use of its technology.

Author contributions

Conception and design of the research: Silva LCA, Werkhauser RP, Carvalho VCV, Montenegro SML. Acquisition of data: Silva LCA, Araújo RM, Soares FCS, Montenegro ST, Carvalho VCV, Montenegro SML. Analysis and interpretation of the data: Silva LCA, Araújo RM, Werkhauser RP, Tashiro T, Carvalho VCV, Montenegro SML. Statistical analysis: Silva LCA, Werkhauser RP, Tashiro T, Carvalho VCV, Montenegro SML. Obtaining financing: Silva LCA, Carvalho VCV, Montenegro SML. Writing of the manuscript: Silva LCA, Carvalho VCV, Montenegro SML. Critical revision of the manuscript for intellectual content: Silva LCA, Araújo RM, Soares FCS, Werkhauser RP, Montenegro ST, Tashiro T, Carvalho VCV, Montenegro SML.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by Proep APQ 1620 4.01/15.

Study Association

This article is part of the thesis of master submitted by Lílian Amorim, from Instituto Aggeu Magalhães (IAM/FIOCRUZ).

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the PROCARDIO/REALCOR under the protocol number 565.461. 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. Silva HS, Moresco RN. Biomarcadores cardíacos na avaliação da síndrome Coronariana Aguda. Scientia Medica. 2011;21(3):132-42
2. Overbaugh KJ. Acute Coronary Syndrome. Am J Nurs. 2009;109(5):42-52.
3. Cavusoglu E, Marmur JD, Yanamadala S, Chopra V, Hedge S, Nazli A, et al. Elevated baseline plasma IL-8 levels are an independent predictor of long-term all-cause mortality in patients with acute coronary syndrome. Atherosclerosis. 2015;242(2):589-94.
4. Apostolakis S, Vogiatzi K, Amanatidou V, Spandidos DA. Interleukin 8 and cardiovascular disease. Cardiovasc Res. 2009;84(3): 353–60.
5. Vogiatzi K, Apotolaskis S, Voudris V, Thomopoilou S, Kochhiadakis, GE, Spandidos DA. Interleukin 8 and Susceptibility to Coronary Artery Disease: a Population Genetics Perspective. J Clin Immunol. 2008;28(4):329-35.
6. Zhang X, Zhang B, Zhang M, Han Y, Zhao Y, Meng Z, et al. Interleukin-8 gene polymorphism is associated with acute coronary syndrome in the Chinese Han population. Cytokine. 2011;56(2):188-91.
7. Zhang M, Fang T, Wang K, Mei H, Lv Z, Wang F, et al. Association of polymorphisms in interleukin-8 gene with cancer risk: a meta-analysis of 22 case–control studies. Onco Targets Ther. 2016 Jun;9:3727-37.
8. Chen J, Ying XM, Huang XM, Huang P, Yan SC. Association between polymorphisms in selected inflammatory response genes and the risk of prostate cancer. Onco Targets Ther. 2016 Jan;9:223-9.
9. Georgitsi MD, Vitoros V, Panou C, Tsangaris I, Aimoniotou E, Gatselis NK, et al. Individualized significance of the −251 A/T single nucleotide polymorphism of interleukin-8 in severe infections. Eur J Clin Microbiol Infect Dis. 2016;35(4):563-70.

10. Behelgardi A, Hosseini SM, Mohebbi SR, Azimzadeh P, Derakhshani S, Karimi K, et al. A Study on Genetic Association of Interleukin-16 Single Nucleotide Polymorphism (rs1131445) With Chronic Hepatitis B Virus Infection in Iranian Patients. Jundishapur J Microbiol. 2015;8(11):e23411.

11. Grönberg C, Asciutto G, Persson A, Fredrikson GN, Nilsson J, Gonçalves I, et al. Endarterectomy patients with elevated levels of circulating IL-16 have fewer cardiovascular events during follow-up. Cytokine. 2016 Sep;85:137-9.

12. Chen W, Zhu WL, Zhang SY, Chen LF, Wang X, Chen TB, et al. Increased Monocytic Expression of Urokinase Receptor in Acute Coronary Syndrome: A Potential Marker of Clinical Instability. Heart. 2012;98(2):E181.

13. Chen Y, Huang H, Pan LA, Zhou B, Zhang L, Leng Z, et al. IL-16 rs11556218 gene polymorphism is associated with coronary artery disease in the Chinese Han population. Clin Biochem. 2011;44(13):1041-4.

14. Huang H, Zeng Z, Zhang L, Liu R, Li X, Qiang O. The association of interleukin-16 gene polymorphisms with susceptibility of coronary artery disease. Clin Biochem. 2013;46(3):241–4.

15. Wu J, Wang Y, Zhang Y, Li L. Association Between Interleukin-16 Polymorphisms and Risk of Coronary Artery Disease. DNA Cell Biol. 2011;30(5):305-8.

16. Tong Z, Li Q, Zhang J, Wei Y, Miao G, Yang X. Association between interleukin 6 and interleukin 16 gene polymorphisms and coronary heart disease risk in a Chinese populationn. J Int Med Res. 2013;41(4):1049-56.

17. Chanock SJ, Thomas G. The devil is in the DNA. Nat Genet. 2007;39(3):283-4.

18. Parra FC, Amado RC, Lambertucci JR, Rocha J, Antunes CM, Pena SD. Color and genomic ancestry in Brazilians. Proc Natl Acad Sci U S A. 2003;100(1):177-82.

19. Andia DC, Letra A, Casarin RCV, Casati MZ, Line SRP, Souza AP. Genetic analysis of the IL-8 gene polymorphism (rs4073) in generalized agressive periodontitis. Arch Oral Biol. 2013;58(2):211-7.

20. Frade AF, Oliveira LC, Costa DL, Costa CH, Aquino D, Van Weyenbergh J, et al. TGFB1 and IL8 gene polymorphisms and susceptibility to visceral leishmaniasis. Infect Genet Evol. 2011;11(5):912-6.

21. Matos MF, Lourenço DM, Orizaka CM, Bajerl JA, Noguti MA, Morelli VM. The role of IL-6, IL-8 and MCP-1 and their promoter polymorphisms IL-6 -174GC, IL-8 -251AT and MCP-1 -2518AG in the risk of venous thromboembolism: A case-control study. Thromb Res. 2011;128(3):216-20.

22. Khosropanah H, Sarvestani EK, Mahmoodi A, Golshah M. Association of IL-8 (-251 A/T) Gene Polymorphism with Clinical Parameters and Chronic Periodontitis. J Dent (Tehran). 2013;10(4):312-8.

23. Tang YJ, Wang JL, Xie KG, Lan CG. Association of interleukin 16 gene polymorphisms and plasma IL16 level with osteosarcoma risk. Sci Rep. 2016;6:34607.

24. Azimzadeh P, Romani S, Mohebbi SR, Kazemian S, Vahedi M, Almasi S, et al. Interleukin-16 (IL-16) gene polymorphisms in Iranian patients with colorectal cancer. J Gastrointestin Liver Dis. 2011;20(4):371-6.

25. Farkas GJ, Hofner P, Balog A, Takács T, Szabolcs A, Farkas G, Mándi Y, et al. Relevance of transforming growth factor-beta1, interleukin-8, and tumor necrosis factor-alpha polymorphisms in patients with chronic pancreatitis. Eur Cytokine Netw. 2007;18(1):31-7.

26. Cengiz M, Yasar DG, Ergun MA, Akyol G, Ozenirler S. The Role of Interleukin-6 and Interleukin-8 Gene Polymorphisms in Non-Alcoholic Steatohepatitis. Hepat Mon. 2014;14(12):e24635.

27. Smith KC, Bateman AC, Fussell HM, Howell WM. Cytokine gene polymorphisms and breast cancer susceptibility and prognosis. Eur J Immunogenet. 2004;31(4):167-73.

28. Gawryszewski VP, Souza MF. Mortality due to cardiovascular diseases in the Americas by region, 2000-2009. Sao Paulo Medical Journal. 132(2):105-10.

29. Dutra DD, Duarte MC, Albuquerque KF, Lima AlS, Santos JS, Souto HC. Cardiovascular disease and associated factors in adults and elderly registered in a basic health unit. J Fundam Care Online. 2016;8 (2):4501-9.

30. Marino BC, Marcolino MS, Reis Júnior RS, França AL, Passos PF, Lemos TR, et al. Epidemiological Profile and Quality Indicators in Patients with Acute Coronary Syndrome in Northern Minas Gerais – Minas Telecardio 2 Project. Arq Bras Cardiol. 2016;107(2):106-15.

31. Shah AS, Anand A, Sandoval Y, Lee KK, Smith SW, Adamson PD, Chapman AR, et al. High-sensitivity cardiac troponin I at presentation in patients with suspected acute coronary syndrome: a cohort study. Lancet. 2015;386(10012):2481-8.

32. Maas AH, Appelman YE. Gender differences in coronary heart disease. Neth Heart J. 2010;18(12):598-602.

33. Magee RL, Lacerda ECT, Borges GFB, Daher GAG, Macedo RG, Nogueira ACC, Brinck AV. Síndrome Coronariana Aguda: uma revisão. Rev Med Saude Brasilia 2012;1(3):174-89

34. Mendelsohn ME, Karas RH. Estrogen and the blood vessel wall. Curr Opin Cardiol. 2018;33(1):95-100.

35. Bray JE, Stub D, Ngu P, Cartledge S, Straney L, Stewart M, et al. Mass Media Campaigns' Influence on Prehospital Behavior for Acute Coronary Syndromes: An Evaluation of the Australian Heart Foundation's Warning Signs Campaign. J Am Heart Assoc. 2015;4(7):e001927.

36. Guedes RF, Melo TE, Lima AP, Guimarães AL, Moreira NBB, Garcia PG.. Análise do perfil lipídico e dos fatores de risco associados a doenças cardiovasculares em acadêmicos da área da saúde de Juiz de Fora. HU Revista. 2016;42(2):159-64.

37. Satti HS, Hussain S, Javed Q. Association of Interleukin-6 Gene Promoter Polymorphism with Coronary Artery Disease in Pakistani Families. Scientific World J. 2013 Dec;2013:538365.

38. Vargas-Alarcon G, Vallejo M, Posadas-Romero C, Juarez-Rojas JG, Martinez-Rios MA, Peña-Duque MA, et al. The -974C>A (rs3087459) gene polymorphism in the endothelin gene (EDN1) is associated with risk of developing acute coronary syndrome in Mexican patients. Gene. 2014;542(2):258-62.

39. Brasil. Ministério da Saúde. Envelhecimento e saúde da pessoa idosa. 2006. [Cited in 2018 Feb 12]. Available from: http://189.28.128.100/dab/docs/publicacoes/cadernos_ab/abcad19.pdf]

40. Feijó MKEF, Lutkmeier R, Ávila CW, Rabelo ER. Fatores de risco para doença arterial coronariana em pacientes admitidos em unidade de hemodinâmica. Rev Gauch Enfer. 2009;30(4):641-47.

41. Rodrigues PH, Oliveira MB, Cazelato L, Chagas EF, Quitério RJ. A influência dos fatores de risco para doenças cardiovasculares sobre a modulação autonômica cardíaca. Rev Aten Saúde. 2016;14(49):34-40.

42. Andrade SM, Telino CJ, Sousa AC, Melo EV, Teixeira CC, Teixeira CK. Oliveira JL, et al. Baixa Prevalência de Eventos Adversos Maiores à Ecocardiografia sob Estresse Físico. Arq Bras Cardiol. 2016;107(2):116-23.

43. Gronberg, C., Bengtsson, E., Fredrikson, G. N., Nitulescu, M., Asciutto, G., Persson, A, Bjorkbacka. Human Carotid Plaques With High Levels of Interleukin-16 Are Associated With Reduced Risk for Cardiovascular Events. Stroke. 2015;46(10):2748-54.

International Journal of Cardiovascular Sciences. 2020; 33(3):263-271

ORIGINAL ARTICLE

QT Interval Dispersion Behavior in Patients with and without Obstructive Coronary Artery Disease Undergoing Exercise Test

Alexandre Maulaz Barcelos,[1] Marcelo Perim Baldo,[2] Sérgio Lamego Rodrigues,[2] José Geraldo Mill[2]

CEAP - Centro de Ensino e Aperfeiçoamento em Pesquisa - Hospital Evangélico de Vila Velha,[1] Vila Velha, ES - Brazil
Universidade Federal do Espírito Santo (UFES),[2] Espírito Santo, ES - Brazil

Abstract

Background: Stress test is used to detect coronary artery disease (CAD). The QTc interval dispersion (dQTc) is an electrocardiographic index of ventricular repolarization heterogeneity. Some researchers have linked transient myocardial ischemia induced by physical exertion with increased heterogeneity of ventricular repolarization measured by dQTc.

Objectives: To study the patterns of dQT in patients with and without chronic obstructive CAD and to define a reliable cutoff point for dQT that could become a diagnostic criterion for myocardial ischemia.

Methods: We retrospectively analyzed the electrocardiogram in resting and in exercise of 63 patients submitted to exercise test and cardiac catheterization. We divided the patients into three groups: true negative (VN), true positive (VP) and false positive (FP). VN: patients with coronary lesion lower than 70% and exercise test without myocardial ischemia; VP: individuals with stenosis greater than 70% in coronary arteries and a test suggestive of myocardial ischemia; FP: people with stenosis lower than 70% in the coronary arteries and stress test with ischemia criteria. Values of $p < 0.05$ were considered statistically significant.

Results: Resting dQTc was not different among the three groups. However, for the dispersion of the QTc interval in exercise was, respectively, 47 ± 17 ms, 72 ± 42 ms, and 61 ± 31 ms for VN, VP and FP ($p = 0.003$).

Conclusions: Obstructive chronic coronary disease patients have an increase in dQTc during exercise. Measurement of dQTc may be helpful in the diagnosis of myocardial ischemia in the stress test. (Int J Cardiovasc Sci. 2020; 33(3):263-271)

Keywords: Coronary Artery Disease/physiopathology; Exercise Test/method; Electrocardiography/method; Myocardial Ischemia; Electrophysiology; QT Dispersion Interval.

Introduction

Stress test has been used in Brazil since 1972 and its sensitivity and specificity for the diagnosis of chronic CAD are 50-72% and 69-74%, respectively.[1-4] The QT interval dispersion (QTD) measurement is considered a promising instrument to improve the diagnostic accuracy of stress test. QTD was defined in the 1990s[5] as the difference between maximal and minimal QT interval duration measured in 12 ECG leads. It has been proposed as a regional marker of ventricular repolarization dispersion (VRD) and correlates with the dispersion of action potentials (AP) in animals and humans.[6] QT interval, measured from the beginning of the QRS complex to the end of the T wave, represents the time it takes for ventricular myocardial cells to depolarize and repolarize.[7] However, U-wave should not be included in the measurement.[8]

During exertion, patients with chronic CAD present increased ventricular repolarization heterogeneity,

Mailing Address: Alexandre Maulaz Barcelos
R. Vênus, s/n - Industrial do Alecrim. Postal Code: 29118-300, Vila Velha, ES – Brazil.
E-mail: alexandremaulazbarcelos@gmail.com

DOI: https://doi.org/10.36660/ijcs.20181068l

Manuscript received on April 06, 2018; reviewed on July 02, 2019; accepted on July 30, 2019.

which is reflected by increased QTD.[9-11] Koide et al.,[12] observed that even when a coronary patient, undergoing stress test, did not present ischemia criteria, the QTD was higher (62 ± 13 ms) compared to patients without coronary disease (40 ± 14 ms). Musha et al.,[13] and col. showed an increase of QTD after exercise, which was not reduced by beta-blockers.[13] Naka,et al.,[14] in a study with infarcted patients, found an increase in QTD due to residual ischemia;however, it did not increase in patients without residual ischemia.

There are several limitations to QT interval measurement technique. Among them, T-P fusion during higher heart-rates and changes in Qt interval rates in relation to men and women[15,16] are worthy of note.

The aims of this study are to evaluate whether the QTD index is sensitive to action potential changes in the presence of stress induced myocardial ischemia, as well as to define a cutoff point for QTD that could become a diagnostic criterion for myocardial ischemia.

Methods

An observational analytical study, where 80 patients underwent exercise testing and coronary angiography (CAT), with a maximum interval of 6 months between the tests. The patients were aged 18 to 80 years. People who had any of the following conditions were excluded from the study: previous acute myocardial infarction (AMI), complete right [RBBB] or left [LBBB] bundle branch block, patients with long QT syndrome; patients with known ventricular dysfunction; unreadable ECG traces or ECG where less than eight electrocradiographic leads were available for QTI measurement.[17] A total sample of 80 patients was defined at the convenience of the researcher.

Treadmill test was performed with an analog-to digital converter of signals, Ergo PC 13 model in Micromed 2.3 version, with a simultaneous acquisition of twelve leads and record with speed of 25 mm/s and amplitude of 10 mm/mV. The protocols used for all patients were individualized aiming at reaching maximum heart rate. The test was considered suggestive of myocardial ischemia in case the patient presented at least onde one the ischemia criteria defined by the III Guidelines on ergometric tests of the Brazilian Society of Cardiology;[18] typical chest pain on exertion;ST-segment elevation or depression, equal to or greater than 1 mm, in relation to baseline ECG. The QT interval of each lead was calculated by the mean of the three beats with less artifact. By using a cursor, one point was marked at the beginning of the QRS complex and another at the end of the T-wave (the point where the T wave returned to the isoelectric line) for each of the three beats.[11] After the measurement, we calculated the mean of the three values found, which would be the value to be considered as the QTI of the mentioned lead. The same procedure was performed for the 12 leads. Thus, for each patient in the study, at least, 24 QT intervals were measured at rest (standing) and 24 on ECG obtained within the first minute of the recovery stage. We decided to "measure the peak stress" within the first minute of the recovery phase in order to minimize the technique's artifacts. At the end of the measurement of the QT intervals of all leads, we marked the highest and the lowest measure found, in the two phases studied: rest and effort. From these values, we calculated the QTI dispersion of these two phases, and also a delta QT dispersion value by determining the difference of QTD between effort and rest.

In order to adjust the QT interval for the corresponding heart rate (HR), we used the Bazett's formula. The adjustment enabled the calculation of the QTc (QT interval dispersion corrected for heart rate), and also the QTc "delta" – the difference between rest-stress QTc intervals. All the electrocardiographic measurements were done by a single observer. Figure 1 shows the sequence to measure a QT interval.

Interobserver variability was determined by measurements performed by a second researcher, who was blinded to the measures obtained by the first observer. The second ECG expert measured the QT interval in 12 patients randomly selected (patients were numbered from 1 to 63, and 12 numbers were raffled). The correlation between the measures was determined by Pearson's correlation coeficiente. The Bland-Altman test was also used to assess interobserver variability (Figure 2).

After catheterization, patients with a coronary stenosis of at least 70% of one or more arteries, or with ≥ 50% stenosis of the left coronary trunk (LCT), were classified as "people with obstructive coronaropathy". In contrast, patients with with stenosis less than 70% in epicardial coronary arteries, or less than 50% in the left coronary trunk, were classified as "without obstructive coronary disease".

The Medcalc software was used for the statistical analysis. The data were expressed in absolute numbers, percentages and standard deviation. The classificatory variables were presented as tables, and the propotions were compared using the chi-square

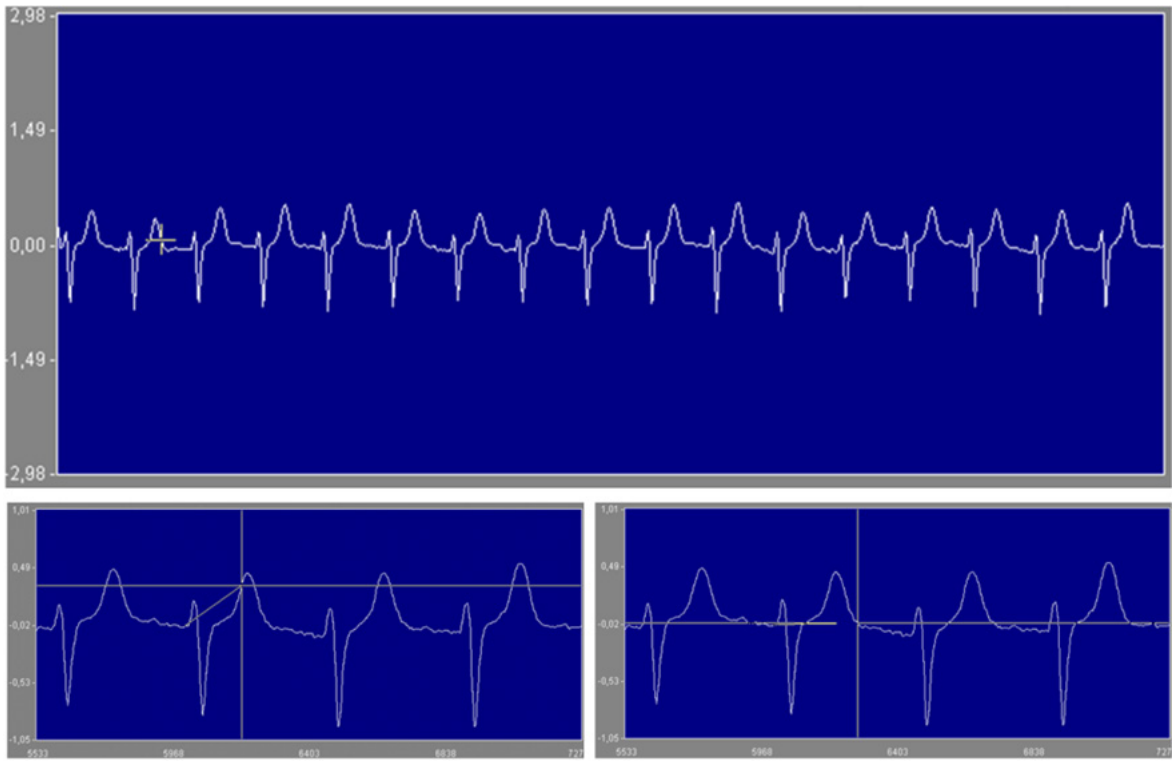

Figure 1 - Measurement sequencing of a QT interval.

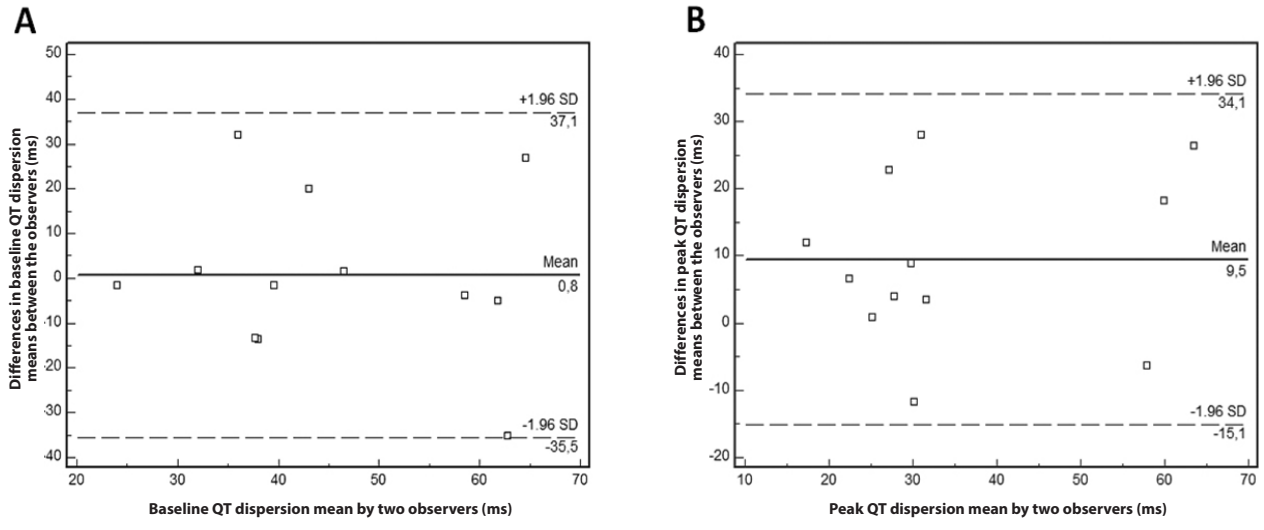

Figure 2 - Reproducibility of QT dispersion measurements before (A) and during (B) effort, assessed using the Bland-Altman method.

test. The Kolmogorov-Smirnov was used to assess the normality of the continuous variables. To identify the best QT dispersion cutoff point for the diagnosis of obstructive coronaropathy, ROC curves were used both for QT dispersion values and for rest and stress QTc. We calculated the QTd, the QTc, and conventional stress test sensitivity and specificity for the diagnosis of chronic obstructive coronaropathy. We also found a QTc delta – the difference between rest-stress QTc intervals, as well as the QT delta - the difference between rest-stress QTd intervals. Subsequently, patients were divided into three groups: true positive (TP) – patients with positive stress test for ischemia and coronary angiography showing stenosis ≥ 70% of at least one major epicardial artery, except for left coronary trunk lesions which were considered to be significant when the obstruction was > 50%. The false positive (FP) group was composed of patients with positive stress test and stenosis less than 70% in at least one major epicardial artery, except for left coronary trunk lesions which were considered to be significant when the obstruction was < 50%. Finally, the true negative (TN) group was composed of negative stress test patients and coronary angiography showing stenosis less than 70% in any epicardial coronary artery, except for left coronary trunk lesions which were considered to be significant when the obstruction was < 50%. $p < 0.05$ was considered to be statistically significant and one-way-variance analysis (ANOVA) was used to compare the three groups. A paired t-test was used to assess the QTc behavior during rest and effort.

All the patients signed the free and clarified term of consent and the research Project was approved by the Ethics Committee on Human Research of Federal University of Espirito Santo (UFES), by the protocol number: 06177412.1.0000.5071.

Results

The difference between the mean QTd values obtained by both observers, at rest, was only 0,8 ± 18,3 ms, which is quite satisfactory. However, we observed some data points of standard deviation away from the mean, which demonstrated the low reproducibility of the measures at rest. The difference between the means obtained by the two observers was 9,5 ± 12,5 ms in peak stress measurements. Additionally, we also found data points of standard deviation away from the mean, which confirmed the low reproducibility of QT dispersion for peak stress measures as well.

The variability between the two observers was also analyzed using Pearson's correlation coefficient. For the baseline value of QTd, the value of "r" found was 0.36 ($p = 0.25$). For the peak QTd, the value of "r" was 0.73 ($p = 0.007$). The correlation between the measures obtained by the two observers was positive weak at rest and positive moderate on exertion. These results indicate a poor reproducibility of QT interval dispersion measures.

Out of the 74 patients initially selected, after we excluded those who presented any of the exclusion criteria, and after the false-positives were removed – because they were of no interest for the research (negative stress test and stenosis greater than 70% in epicardial arteries, except for trunk lesions which were considered to be significant when the obstruction was > 50%), there were 63 patients who fulfilled the criteria to be in the three research groups: TP, FP and TN. The three groups studied (TP, FP and TN) were similar in relation to general characteristics (Table 1), including comorbidities and medicaments in use.

The cutoff value found with the ROC curve was the point where better QTd and QTc sensitivity and specificity for the diagnosis significant coronaropathy were achieved (46ms and 57ms, respectively). Regarding

Table 1 - General characteristics of the groups

	TP (n = 26)	FP (n = 23)	TN (n = 14)	p-value
Age (years)	58 ± 10	54 ± 12	56 ± 11	0.43
Male sex (%)	81%	71%	71%	0.453
Diabetes mellitus (%)	27%	13%	7%	0.213
Arterial hypertension (%)	58%	58%	79%	0.372
Beta-blockers (%)	23%	33%	21%	0.633
ACEI/ARB (%)	42%	21%	21%	0.188
Statins (%)	12%	8%	21%	0.199
Calcium antagonists (%)	12%	0%	29%	

Values expressed as mean ± SD or percentages; TP: true positive; FP: false positive; TN: true negative.

the stress QTd, the sensitivity was 44.4% and the specificity was 81.6% (AUC 0.585;CI 95% 0.465-0.699) with a cutoff of 46 ms. For stress QTc, the sensitivity was 58.3% and the specificity was 63.2% (AUC 0.593;CI 95% 0.472-0.706) with a cutoff of 57 ms. In relation to the sensitivity and specificity values of the traditional treadmill test, and considering the presence of ST segment depression or typical chest pain on exertion, we found a sensitivity of 72% and a specificity of 32% in our sample. Since the confidence intervals found for the QTd and QTc cutoff values included the 0.5 value, we decided not to aggregate the QT dispersion values into the traditional stress test, because any improvements in the sensitivity and specificity that we could possibly find would not have been reliable.

When we analyzed the three groups formed (TN, TP and FP), the following was found: the mean values of QT dispersion at rest did not show statistically significant difference between the three groups. Respectively, 58 ± 30 ms, 47 ± 22 ms and 43 ± 19 ms, for the TN, TP and FP groups (p = 0.172). In addition, we did not observe significant difference between the mean values of the QTc dispersion at rest: 67 ± 40 ms, 55 ± 26 ms and 49 ± 21 ms, respectively, for the TN, TP and FP groups (p = 0,163). Thus, we moved on to analyze the mean QT dispersion values found between the three groups during effort. Similarly to what happened in relation to QT dispersion at rest, we found close mean values with no statistical difference between the three groups: 32 ± 11 ms, 48 ± 28 ms and 42 ± 22 ms, respectively, for the TN, TP and FP groups (p = 0.124). However, when we analyzed the data of QTc dispersion of effort, we verified that the values of QTc between the three groups were different: TN (47 ± 17 ms), TP (72 ± 42 ms) and FP (61 ± 31 ms), with p = 0.003. When we compared TN and TP, we found p < 0.05; when comparing TN and FP, we also found p < 0.05; however, when VP and FP were compared, we found p > 0.05 (Table 2).

In order to better assess the changes in stress induced coronary depolarization, we created a delta QT dispersion value (ΔQTD) which was obtained by the following equation: ΔdQT= QTd stress – QTd rest. Likewise, we obtained a delta value of QTc dipersion by a similar equation: ΔdQTc = QTc stress – QTc rest. The ΔdQT was −25 ± 33 ms in the TN group, 1 ± 27 ms in the TP and −2 ± 23 ms in the FP group, with statistical difference between the three groups, with p = 0.013. Comparing TN and TP, we found p < 0.05;the same was observed when TN was compared with FP (p < 0.05);in contrast, the comparison between TP and FP showed p > 0.05. The mean ΔQTc dispersion was −20 ± 45 ms in the TN group, 17 ± 40 ms in the TP group and 11 ± 30 ms in the FP group. Again, the same "p" value of 0.013 was found between the three groups, as well as the same values of "p" for the other comparisons: TN vs VP (p < 0.05), VN vs FP (p < 0.05) and VP vs FP (p > 0.05). We did not find any statistical difference between TP vs FP. Due to the statistical difference found between the three groups, in relation to the mean values of ΔQTc, we decided to illustrate the behavior of QTc dispersion from rest to stress peak in the three groups. Figures 3, 4 and 5 show the behavior of the three groups.

Table 2 - Clinical and electrocardiographic variables during stress test

	TP	FP	TN	p-value
Number of patients	26	23	14	
Rest HR (bpm)	77 ± 13	79 ± 11	79 ± 14	p = 0.922
Peak HR (bpm)	134 ± 15	131 ± 21	128 ± 22	p = 0.637
Peak SP (mmHg)	171 ± 21	173 ± 39	193 ± 29	p = 0.071
Chest pain on exertion (%)	53%	45%	0	
ST depression (%)	88,40%	79,20%	0	
Pain with ST depression (%)	42,3%	25%	0	
Rest QTd (ms)	47 ± 22	43 ± 19	58 ± 30	p = 0.172
Rest QTc (ms)	55 ± 26	49 ± 21	67 ± 40	p = 0.163
Peak QTd (ms)	48 ± 28	42 ± 22	32 ± 11	p = 0.124
Peak QTd (ms)	72 ± 42	61 ± 31	47 ± 17	p = 0.003
ΔQTD (ms)	1 ± 27	−2 ± 23	−25 ± 33	p = 0.013
ΔQTDc (ms)	17 ± 40	11 ± 30	−20 ± 45	p = 0.013

QTd: QT dispersion; QTc: QT dispersion corrected for heart rate; ΔQTD: Stress peak QT dispersion minus rest QT dispersion; ΔQTDc: QT dispersion corrected for stress peak HF minus QT dispersion corrected for HF at rest.

Discussion

The aim of this study was to assess the relationship between QT interval dispersion and chronic CAD. The focus of our investigation was to evaluate the feasibility

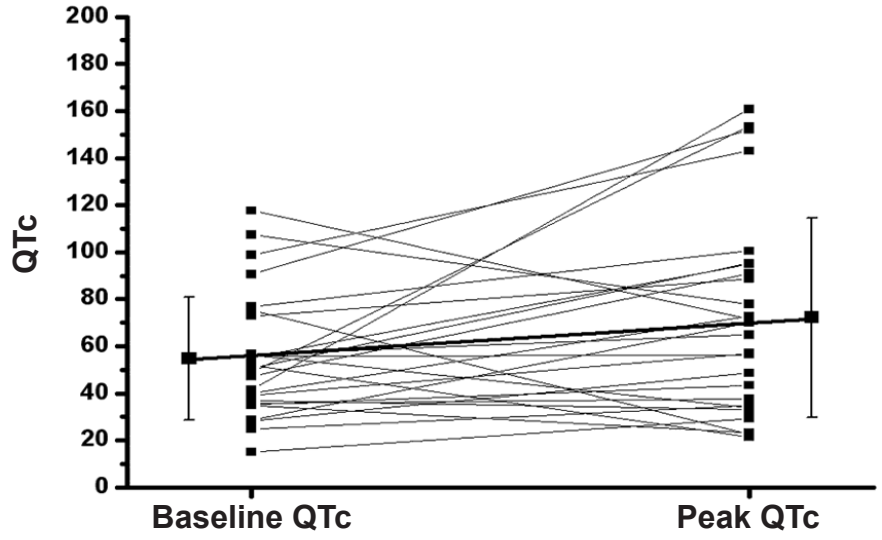

Figure 3 - QTc evolution in the true positive group from rest (baseline QTc dispersion) to effort (peak QTc dispersion) conditions.

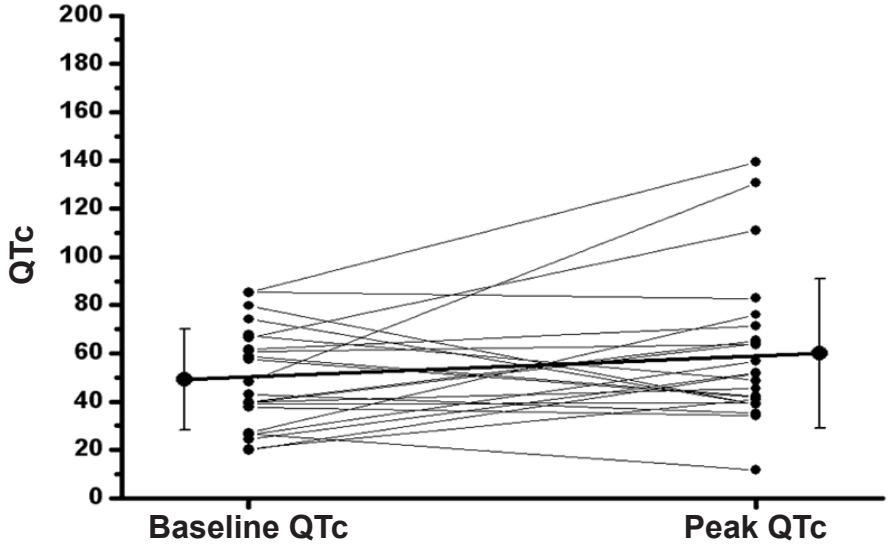

Figure 4 - QTc evolution from rest (baseline QTc) to effort (peak QTc) conditions in the false positive group.

of using the QTd (within the first minute of recovery and/or rest) for the diagnosis of significant coronary disease. Based on previous studies, we hypothesized that coronary obstruction would lead to prolonged action potential in the ischemic region, and that such increase could be identified by the QTd. Actually, it would reflect in theory the difference between repolarization in the ischemic region compared to the non-ischemic in the ventricular syncytium.

The first result that will be discussed concers the reproducibility of QT dispersion measurements. One of the major problems concerning QT interval measurements is the difficulty in obtaining acceptable interobserver variability. In our study, interobserver

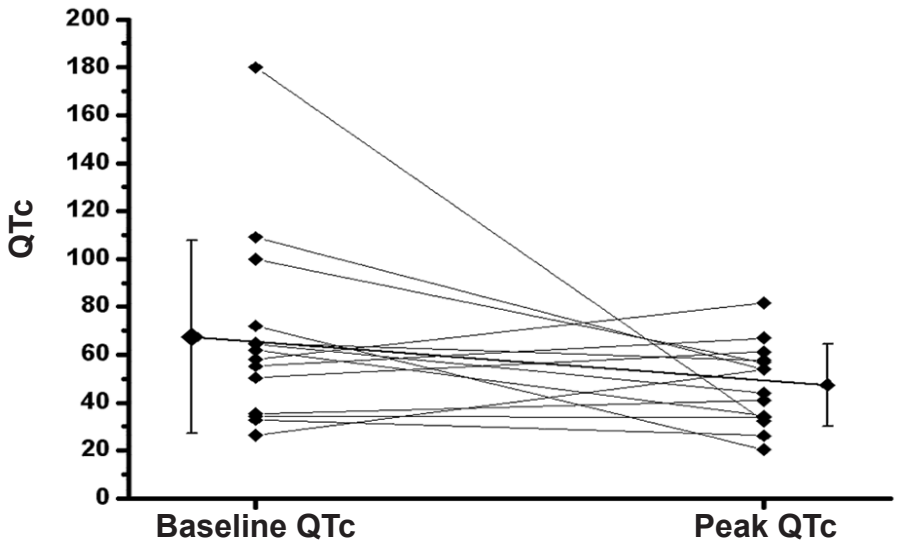

Figure 5 - QTc evolution in the true negative group from rest (baseline QTc) to effort (peak QTc) conditions.

reproducibility was weak. Our impression is that, even with the measurements being performed with more modern software, the problem involving the reproducibility of QT intervals measurements remains a considerable one.

With the results of catheterization, QT dispersion, QTc and stress test, we built ROC curves in order to find the possible cutoff values of QTd and and stress-rest QTc, so as to subsequently calculate the sensitivity and specificity of QTd for the diagnosis of chronic CAD. We did not achieve a minimaly satisfactory ROC curve for QTd and QTc at rest. For QT and QTc dispersion of effort, we obtained ROC curves somewhat better than those obtained at rest, and we found cutoff values for QTd (46 ms) and QTc (57 ms). As for the sensitivity and specificity of stress QTd and QTc it is possible to say that they were comparable to the traditional stress test ischemic criteria. However, what really called attention, was the low specificity of the classical diagnostic criteria of exercise induced ischemia in our sample (32%). On the other hand, the sensitivity was 72%. The high false-positive rate was quite high. We observed that most of the false-positive results were found in the presence of segment depression without a concomitant stenosis of at least 70%. The most plausible explanation found lies in the arbitrariness of considering as the possible cause of ischemia only stenosis with obstruction greater than 70%. Smaller plaques, but under the effect of vasoconstriction substances, can cause ischemia. Another factor to be considered is the possibility of microcirculation disease in patients without significant disease of large coronary arteries. Finally, we must consider that the degree quantification of coronary obstruction made by the doctor responsible for the catheterization is performed by visual method only and, hence, it is observer-dependent.

When we analyzed the data from the three groups formed: true positive (TP), false positive (FP) and true negative (TN), heart rate (HR) and systolic pressure (SP) at stress peak were not statistically different between the three groups (Tabble 2). The incidente of typical chest pain and ST depression at peak stress were higher among the false-positive and true-positive groups, and was not present in the TN group, as we already expected. In relation to the QT dispersion and QTc dispersion at rest, there was no significant statistical difference between the three groups. In contrast, stress QTc was significantly higher among the TP and FP groups, compared with the TN group. The TP and FP groups behaved so similarly that made us wonder about the real importance of considering "people with significant coronary artery disease" only those patients with stenosis of at least 70% in epicardial arteries, or 50% or more in the left coronary trunk. We can speculate that if myocardial perfusion scintigraphy had been performed, instead of cardiac catheterization, as gold standard for significant CAD, it is possible that our results would have been similar to those

obtained by Stoletniy and col.8. These authors showed that the QTc increased from rest to stress in patients with ischemia documented by myocardial scintigraphy, and that it did not increase from rest to stress peak in patients without myocardial scintigraphy documented using radioisotope techniques. We speculate that QTc is, ultimately, a marker of myocardial ischemia, with no strict connection with the degree of obstruction in large coronary arteries.

The QTc delta also showed significant statistical difference between the groups. However, in order to test the theory that supports the concept of QTd, we decided to scketch a line graph that represented each individual in the three groups. Our concern was that the QTc and QTc delta values would show only the statistical difference between the means of the three groups (extreme QTc values of few individuals of one group can affect the mean and not necessarily represent the behavior of the rest to stress condition variable). Corroborating the results of the QTc dispersion of effort, nineteen patients from the TP group presented increased QTc from rest to stress conditions (Figure 3), whereas seven individuals showed a reduction. In contrast, in the TN group, five people presented increased QTd and nine reductions (Figure 5). The FP group maintained similar behavior as the TP group. In FP, fourteen patients increased the QT dispersion and nine reduced it (Figure 4). In order to statistically test the behavior of each group in relation to the QTc dispersion of effort and at rest, we used a paired T-test for each group, and obtained significant difference between the TP group means from rest to stress conditions, and a a trend to increased QTc in the FP group. The TN negative group did not show significant changes between the QTc pre- and postexercise means. We conclude that QTc behaves, predominantly, with an increase on exertion in patients with myocardial ischemia;and tends not to change significantly in patients without ischemia.

Our study has some limitations that should be pointed out. First, our sample was small so we could not obtain a highly reliable cutoff point for QTc. Still, we must remember that our QTc cutoff point was quite similar to the ones found by other authors. Secondly, the methodology we used to measure the QTI – as far as we know - is unprecedented in the literature. Thus, our data must be confirmed by other similar studies. Our results can only be considered for a coronary population with no previous AMI or ventricular dysfunction. Finally, this is a database retrospective study with all the limitations inherent to this type of study.

Conclusions

Based on our results, we believe that QT dispersion – is spite of being a "crude" marker of ventricular repolarization heterogeneity – is sensitive to stress-induced myocardial ischemia and can aid in the diagnosis of chronic CAD.

Author contributions

Conception and design of the research: Barcelos AM, Mill JG. Acquisition of data: Barcelos AM, Rodrigues SL, Mill JG. Analysis and interpretation of the data: Barcelos AM, Baldo MP,Rodrigues SL, Mill JG. Statistical analysis: Barcelos AM, Baldo MP, Rodrigues SL, Mill JG. Obtaining financing: Barcelos AM. Writing of the manuscript: Barcelos AM. Critical revision of the manuscript for intellectual content: Barcelos AM, Baldo MP, Rodrigues SL, Mill JG.

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 Alexandre Maulaz Barcelos, from CEAP - Centro de Ensino e Aperfeiçoamento em Pesquisa - Hospital Evangélico de Vila Velha.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the *Hospital Universitário Cassiano Antônio de Moraes* under the protocol number CAAE: 06177412.1.00007051. 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. Detrano R, Gianrossi R, Froelicher V. The diagnostic accuracy of the exercise electrocardiogram: a meta-analysis of 22 years of research. Prog Cardiovasc Dis. 1989;32(3):173-206.
2. Gianrossi R, DetranoR, Mulvihill D, Lehmann K, DubachP, Colombo A, et al. Exercise-induced ST depression in the diagnosis of coronary artery disease: a meta-analysis. Circulation. 1989;80(1):87-98.
3. LadenheimML, KotlerTS, PollockBH, BermanDS, DiamondGA. Incremental prognostic power of clinical history, exercise electrocardiography, and myocardial perfusion scintigraphy in suspected coronary artery disease. Am J Cardiol. 1987;59(4):270-7.
4. Ellestad MH, Wan MK. Predictive implications of stress testing. Follow-up of 2700 subjects after maximum treadmill stress testing. Circulation. 1975;51(2): 363-9.
5. Day CP, McComb JM, Campbell RW. QT dispersion: an indication of arrhythmia risk in patients with long QT intervals. Br Heart J. 1990;63(6):342-4.
6. Zabel M, Portnoy S, Franz MR. Electrocardiographic indexes of dispersion of ventricular repolarization: anisolated heart validation study. J Am Coll Cardiol. 1995;25(3):746-52.
7. Kautzner J. QT interval measurements. Card Electrophysiol Rev. 2002;6(3):273-7.
8. Bonow RO, Mann DL, Zipes DP, Libby P. Braunwald's heart disease: a textbook of cardiovascular medicine. 7th. Philadelphia: W.B. Saunders; 2005. p. 2183.
9. Stierle U, Giannitsis E, Sheikhzadeh A, Krüger D, Schmücker G, Mitusch R, et al. Relation between QT dispersion and the extent of myocardial ischemia in patients with three-vessel coronary artery disease. Am J Cardiol. 1998;81(5):564-8.
10. Stoletniy LN, Pai RG. Valueof QT dispersion in the interpretation of exercise stress test in women. Circulation. 1997;96(3):904-10.
11. Sporton SC, Taggart P, Sutton PM, Walker JM, Hardman SM. Acute ischemia: a dynamic influence on QT dispersion. Lancet. 1997;349(9048):306-9.
12. Koide Y, Yotsukura M, Yoshino H, Ishikawa K. Usefulness of QT dispersion immediately after exercise as an indicator of coronary stenosis independent of gender or exercise-induced ST-segment depression. Am J Cardiol. 2000;86(12):1312-7.
13. Musha H, Kunishima T, Awaya T, Iwasaki T, Nagashima J, Nakamura T, et al. Influence of exercise on QT dispersion in ischemic heart disease. Jpn Heart J. 1997;38(2):219-26.
14. Naka M, Shiotani I, Koretsune Y, Imai K, Akamatsu Y, Hishida E, et al. Occurrence of sustained increase in QT dispersion following exercise in patients with residual myocardial ischemia after healing of anterior wall myocardial infarction. Am J Cardiol. 1997;80(12):1528-31.
15. Chauhan VS, Krahn AD, Walker BD, Klein GJ, Skanes AC, Yee R. Sex differences in QTc interval and QT dispersion: dynamics during exercise and recovery in healthy subjects. Am Heart J. 2002;144(5):858-64.
16. Kligfield P, Lax KG, Okin PM. QT interval-heart rate relation during exercise in normal men and women: definition by linear regression analysis. J Am Coll Cardiol. 1996;28(6):1547-55.
17. Surawicz B, Knilans TK. Chou's electrocardiography in clinical pratice: adult & pediatric. 5nd. Philadelphia: W.B. Saunders; 2001. p. 709.
18. Meneghelo RS, Araújo CG, Stein R, Mastrocolla LE, Albuquerque PF, Serra SM, et al. Sociedade Brasileira de Cardiologia. III Diretrizes da Sociedade Brasileira de Cardiologia sobre Teste Ergométrico. Arq Bras Cardiol. 2010;95(5 Suppl 1):1-26.

ORIGINAL ARTICLE

Analysis of Adherence to Antihypertensive Drug Treatment in an Argentinean Cohort

Walter Gaston Espeche,[1] Rodrigo Sabio,[2] Alejandro Diaz,[3] Roberto Parodi,[4] Carlos Enrique Leiva Sisnieguez,[5] Roberto Antonio Flores,[6] Silvia Poppe,[7] Javier Altube,[2] Diego Grimaldi,[2] Martin Rogelio Salazar[5]

Interzonal General Hospital of Acutes Jose de San Martin,[1] Buenos Aires - Argentina
Hospital Calafate,[2] Santa Cruz - Argentina
CONICET Tandil,[3] Buenos Aires - Argentina
Universidad Nacional de Rosario,[4] Rosario - Argentina
Hospital Interzonal General de Agudos General San Martin,[5] La Plata - Argentina
Hospital de Santiago del Estero,[6] Santiago del Estero - Argentina
Hospital General de Agudos Juan A Fernandez,[7] Buenos Aires - Argentina

Abstract

Background: Adherence to antihypertensive medication is a major challenge in the management of hypertension, and non-adherence is an important barrier to effective management of hypertension.

Objectives: To determine the adherence rate to hypertensive drug treatment and the factors that influence non-adherence in a cohort of the Argentinean population.

Methods: A multicenter cross-sectional study was conducted in eight cities of Argentina. Consecutive hypertensive patients seen in general practice offices, receiving pharmacological treatment for at least six months were included. Blood pressure measurements were performed by physicians during the patient visit. The level of adherence was assessed using the Morisky questionnaire, and patients were divided into non-adherent and adherent. Continuous variables were compared using independent t-test. Categorical variables were compared using the χ^2 test. To identify the variables independently associated with non-adherence, a forward stepwise binary regression logistic model was performed, and the results expressed as odds ratio (OR) with 95% of confidence interval. All tests were two-tailed, and p-values < 0.05 were considered statistically significant.

Results: A total of 852 individuals (52% women, 62 ± 13 years) were included. The main reason for lack of adherence was forgetfulness of medication intake and errors in the time of intake (~ 40% in both). Individuals with more cardiovascular risk factors (smoking, diabetes, dyslipidemia and previous cardiovascular events) had lower adherence to antihypertensive treatment, and considerably younger (~ five years younger).

Conclusions: Adherence rate to antihypertensive drug treatment in our study group was higher than the one reported in previous studies, and the main reason for non-adherence was forgetfulness of medication intake. (Int J Cardiovasc Sci. 2020; 33(3):272-277)

Keywords: Hypertension/epidemiology; Risk Factors; Antihypertensive Agents; Cross-Sectional Study.

Introduction

Hypertension contributes to the global burden of cardiovascular disease and premature morbidity and mortality.[1] The ability of pharmacological treatment of hypertension to reduce the risk of cardiovascular events and decrease morbidity and mortality is well established.[2,3] Adherence to antihypertensive medication is a major challenge that clinicians often face in the management of hypertension.[4] Moreover, non-adherence is the main obstacle to controlling hypertension in the community and a significant barrier to an effective management.[5-7] Good adherence is therefore crucial to improve hypertension control rates and prevent complications such as stroke, coronary artery disease, aneurysms and heart failure.[8,9]

Mailing Address: Walter Espeche
General Interzonal Hospital Specialized in Acutes San Martin - Clinica Medica - 1 y 70, La Plata, B1904CFU - Argentina
E-mail: wespeche@gmail.com

DOI: https://doi.org/10.36660/ijcs.20190069

Manuscript received April 05, 2019; revised manuscript August 05, 2019; accepted August 27, 2019.

Medication adherence is defined by the World Health Organization (WHO) as "the degree to which a person's behavior corresponds with the agreed recommendations from a health care provider."[10] The WHO estimates the prevalence of non-adherence to antihypertensive medication to be 30-50%, depending on differences in drug-class, type of prevention and methods used to measure adherence.[6,7,11] In Argentina, a study based on a non-population sample showed a rate of adherence of ~26%.[12] Remarkably, non-adherence was associated with higher cardiovascular risk.[13]

Factors that influence adherence could be classified into five dimensions: 1. patient-related factors (inadequate beliefs or skills), 2. socioeconomic-related factors (poor health literacy or low social support), 3. condition-related factors (presence of comorbidities), 4. therapy-related factors (complex drug regimen) and 5. health system/health-care team-related factors (inadequate communication with health-care provider).[2]

There are direct and indirect methods to assess adherence. While direct methods have the advantage of having greater accuracy, the cost, availability, and accessibility of these methods make their use unlikely in current practice. Conversely, indirect methods, such as the Morisky-Green test, are easy to use in daily medical practice (Table 3).[14] Thus, this test could be used to evaluate adherence in real-world settings.

The aim of this study was to determine the prevalence of adherence in hypertensive patients treated by physicians in several cities in Argentina.

Methods

A multicenter cross-sectional study was conducted in eight cities of Argentina (Tandil, La Plata, El Calafate, Santiago del Estero, San Miguel de Tucumán, Rosario, Misiones and Buenos Aires) between March and August 2018 using a prospectively designed protocol. Each city was represented by a single centre. These cities are the capitals or the most important cities of six provinces (Buenos Aires, Santiago del Estero, Santa Fe, Santa Cruz, Tucuman and Misiones), in the North, South and Central regions of the country.

The study was conducted on consecutive hypertensive patients seen in the general practice office who had been under pharmacological treatment for at least six months.

Blood pressure (BP) measurements were performed by the physician in a single visit (regardless of the purpose of the visit), using an OMRON HEM 705 CP device (OMRON HEALTHCARE Co., Kyoto, Japan). Two measures were taken, with a one-minute interval between measurements, and the mean of the measures was defined as office blood pressure. Body weight was determined with subjects wearing light clothes and no shoes. Height was measured without shoes using a metallic tape, and body mass index (BMI) was calculated. In addition, history of dyslipidemia, diabetes, cardiovascular diseases, and smoking was recorded.

The level of adherence was assessed using the Morisky questionnaire.[14] A non-adherent patient was defined as a patient who answered positively to any one of the questions. Controlled hypertensive patients were defined as those individuals whose BP was < 140-90 mmHg. The type and number of antihypertensive drugs and the use of fixed-dose combinations were recorded. The patients willing to participate signed an informed consent form.

Individuals were divided into controlled and uncontrolled hypertension using the traditional definition[4] and in "non-adherent" and "adherent" according to the Morisky test.

Statistical analysis

The study sample had a normal distribution determined by Test Shapiro Wilk. Baseline continuous variables (age, BMI, systolic BP, and diastolic BP) were expressed as mean ± standard deviation (SD) and were compared using an independent t-test. Categorical variables (sex, current smokers, adherence, diabetes, dyslipidemia, hypertension control, and previous cardiovascular event) were expressed as percentages and compared using the χ^2 test.

To identify the variables independently associated with non-adherence, a forward stepwise binary regression logistic model was performed and the results expressed as odds ratio (OR) with 95% of confidence interval (95% CI).

All tests were two-tailed, and P values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS 18.0.

Results

A total of 862 individuals aged 61 ± 14 years of age, 53% women, from the eight cities (nearly 100 individuals per center) were included. Most patients (79,1%) had health insurance and similar socioeconomic

characteristics. All individuals completed high school. Ten patients were excluded due to lack of consent or blood pressure measurements.

Clinical characteristics of the remaining 852 patients are summarized in Table 1. There were no differences in age, systolic BP, number of drugs used, BMI, previous cardiovascular events, smoking and control of hypertension between men and women. Global adherence to treatment was also not different between men and women, 61.3% and 63.1%, respectively (p = 0.444).

Table 2 shows that individuals who had controlled hypertension were more adherent to treatment (69.3% vs. 53.3%, p < 0.001). Also, they used more fixed-doses combinations of antihypertensive drugs (p < 0.001) and had lower BMI (p < 0.001).

Inhibitors of the renin-angiotensin system (angiotensin receptor antagonists and angiotensin-converting enzyme inhibitors) were the most frequently used antihypertensives (46.8%), followed by beta-blockers, calcium channel blockers and diuretics (6.9%, 2.4%, and 1.0% respectively). Diuretics were the most commonly used drugs as the second drug (22.1%), and 13.5% of the patients used three or more antihypertensive drugs.

The most frequent reasons for lack of adherence were carelessness in the time of intake and forgetfulness of the medication intake. Remarkably, only a minority was not adherent due to adverse drug effects (Table 3).

As shown in Table 4, the non-adherent group was younger, had higher BP values, lower number of never-smokers, and higher frequency of previous cardiovascular events. Although there were no differences in BMI between adherent and non-adherent subjects, more obese

Table 1 - Characteristics of the sample by sex

	Women n = 444	Men n = 408	p-value
Age (years)	62 ± 13	61 ± 12	0.346
SBP (mmHg)	138 ± 18	139 ± 18	0.458
DBP (mmHg)	82 ± 11	84 ± 12	0.002
BMI (Kg/m²)	29.7 ± 6.5	28.8 ± 5.0	0.149
Controlled hypertension (%)	43.0	46.1	0.369
Hypercholesterolemia (%)	35.1	44.1	0.001
Diabetes mellitus (%)	21.8	29.2	0.026
Smoking (%)	12.8	13.2	0.553
Previous cardiovascular event* (%)	5.8	8.0	0.597
Number of antihypertensive drugs	1.6 ± 0.8	1.6 ± 0.8	0.174
Fixed-dose drug combinations(%)	16.0	14.4	0.541
Adherence (%)	63.1	61.3	0.444

**acute myocardial infarction, stroke; SBP: systolic blood pressure; DBP: diastolic blood pressure.*

Table 2 - Characteristics of patients divided into controlled or uncontrolled hypertension

	Controlled hypertension n = 379	Uncontrolled hypertension n = 473	p-value
Age (years)	62 ± 15	60 ± 13	0.043
BMI (Kg/m²)	28.1 ± 5.5	31.0 ± 6.4	< 0.001
Hypercholesterolemia (%)	37.2	42.2	0.137
Diabetes mellitus(%)	22.2	29.3	0.018
Smoking (%)	11.4	15.0	0.228
Previous cardiovascular event* (%)	5.3	9.5	0.018
Number of antihypertensive drugs	1.7 ± 0.8	1.5 ± 0.8	0.002
Fixed-dose drug combinations(%)	14.8	9.8	0.027
Adherence (%)	69.3	53.3	< 0.001

BMI: body mass index.

patients (BMI > 35 kg/m²) were less adherent than the rest of the sample. The use of fixed-dose combination antihypertensives was more frequent in adherent than non-adherent patients (p < 0.001).

Table 3 - Reasons for lack of adherence and percentage of positive responses in the Morisky-Green-Levine test

Questions	Positive answers (%)
1. Do you ever forget to take medications for your hypertension?	15.8
2. Are you careless with the time you should take the medication?	25.6
3. When you are well, do you stop taking the medication?	4.5
4. If you ever feel bad, do you stop taking it?	2.0

1-2. Execution. 3-4. Short persistence.

Table 4 - Characteristics of patients by adherence or not to pharmacological treatment

	Adherence n = 530	Non-adherence n = 322	p-value
Age (years)	63 ± 13	57 ± 15	< 0.001
SBP (mmHg)	136 ± 17	142 ± 19	< 0.001
DBP (mmHg)	80 ± 11	85 ± 12	< 0.001
BMI (Kg/m²)	29.0 ± 5.5	29.7 ± 6.8	0.094
Hypercholesterolemia (%)	41.1	36.6	0.194
Diabetes mellitus(%)	23.4	28.5	0.092
Never-smoking (%)	83.0	76.7	0.024
Previous cardiovascular event* (%)	5.6	9.6	0.029
Number of antihypertensive drugs	1.7 ± 0.8	1.5 ± 0.8	0.056
Fixed-dose drug combination (%)	17.4	4,7	< 0.001

SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index

In the logistic regression analysis, previous cardiovascular event was independently associated with lack of adherence (OR = 3.01 95%CI 1.53-5.91). Conversely, fixed-dose drug combinations (OR = 0.22 95%CI 0.12-0.40) and older age (OR = 0.97 95%CI 0.96-0.0.98) were factors associated with higher adherence.

Discussion

In our study the prevalence of individuals adherent to antihypertensive medication (62.2%) was greater than that previously published using the same test (the Morisky scale).[17] In most previously published studies, adherence to pharmacological treatment was evaluated using different direct and indirect tests, and consequently, comparisons between studies are difficult.

It is of note that the prevalence of hypertensive patients with controlled hypertension in this study, 45.4%, was higher than those reported in other studies performed in Argentina (7-43%).[15] However, since all patients included were treated with antihypertensive drugs, the comparison of the level of control of hypertension between different sample populations is not adequate.

As expected, individuals with controlled BP show a higher adherence rate (69.3% vs 53.3% p < 0.001). Interestingly, the use of fixed-dose combination was associated with both higher rates of adherence and higher rates of BP control. Although, in theory, the use of more antihypertensive drugs could be related to lower adherence, in this study the number of drugs did not differ significantly between adherent vs. non-adherent group. Since multiple drug treatments are often required in hypertension control,[16] fixed-dose drug combination may be an adequate approach to the "more drugs *vs*. better adherence" dilemma.

Analyzing the variables related to adherence, never-smoking was protective factor. We can hypothesize that avoiding the initiation of tobacco use has not only a beneficial effect on the prevention of chronic diseases, but also an indirect effect on improving adherence. Indeed, the non-adherent group had more frequent previous history of cardiovascular events. This could represent reverse causality and highlight that improving adherence in adult patients is a very difficult task.

Regarding the reasons of non-adherence to antihypertensive drug treatment, Burnier et al.[6] identified two different mechanisms: 1-short persistence, i.e., when the patients ceased their engagement with the dosing

regimen on their own initiative (an act that is inherently willful, not arising from forgetfulness). 2-lapses in implementation (or execution), which is a consequence of forgetfulness or negligence. Therefore, knowing and being able to differentiate between the two types of adherence (persistence or execution) would allow formulating specific strategies aimed to improve one of the main reasons why hypertension is not adequately controlled.[16-22] In our study, the lack of adherence was mostly due to forgetfulness in taking medications or in the time of intake (~ 40% to both). Thus, the use of reminders such as alarms, telemedicine, prescription of fixed combinations and less complex regimens could improve adherence in our population.

Our study had some limitations. First, our cross-sectional design precluded the assessment of temporality; rather, we could only obtain associations. Second, adherence was assessed using only one questionnaire – the Morisky scale (only) – which has not been validated to the Argentinean population. However, the instrument had been used in previous studies in our country.[23] The use of a second scale to measure medication adherence would have improved the reliability of our findings. Third, predictors of non-adherence such as a poor patient-provider relationship and time of treatment were not evaluated in this study. Fourth, although this study was carried out in eight cities of different provinces, Argentina is a very large country and a study that covered a greater number of cities, would have greater representation. However, the prevalence of hypertension control was similar to that reported in a previous study conducted in Argentina.[12] Finally, since hypertension control was determined based on BP office values, the possible white coat effect cannot be ruled out. Thus, despite these limitations, our study provides an estimation of non-adherence in an Argentinean cohort.

Conclusions

In conclusion, adherence rate to antihypertensive drug treatment was higher than the one reported in the literature, but still deficient. The main reason for non-adherence to pharmacological treatment was forgetfulness of medication intake. Therefore, differentiating the two types of adherence (persistence and execution) would allow formulating specific strategies aimed to improve the main reasons why hypertension is not adequately controlled. Finally, the lack of adherence was an important issue in patients with established cardiovascular disease.

Author contributions

Conception and design of the research: Sabio R, Diaz A. Acquisition of data: Parodi R. Analysis and interpretation of the data: Leiva CES. Statistical analysis: Leiva CES. Writing of the manuscript: Espeche WG, Salazar MR. Critical revision of the manuscript for intellectual content: Grimaldi D, Poppe S, Altube J. In old de conception: Salazar MR and Espeche WG.

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 Comitefyth under the protocol number EMA1. 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. A global brief on hypertension. Silent killer, global public health crisis. Geneva: World Health Organization; 2013.
2 Sabate E. Adherence to long term therapies. Evidence for action. Geneva: World Health Organization; 2003.
3. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009 May 19;338:b1665.
4. ManciaG, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013;31:1281-1357.
5. van Veen WA. Treatment adherence in hypertension: problems and research. J R Coll Gen Pract Occas Pap. 1980 Jul;(12):22-5.
6. Burnier M, Wuerzner G, Struijker-Boudier H, Urquhart J. Measuring, analyzing, and managing drug adherence in resistant hypertension. Hypertension. 2013;62(2):218-25.
7. van der Laan DM, Elders PJM, Boons CCLM, Beckeringh JJ, Nijpels G, Hugtenburg JG. Factors associated with antihypertensive medication nonadherence: a systematic review. J Hum Hypertens. 2017;31(11):687-94.
8. Agbor VN, Essouma M, Ntusi NAB, Nyaga UF, Bigna JJ, Noubiap JJ. Heart failure in sub-Saharan Africa: a contemporaneous systematic review and meta-analysis. Int J Cardiol. 2018 Apr 15;257:207-15.
9. Nyaga UF, Bigna JJ, Agbor VN, Essouma M, Ntusi NAB, Noubiap JJ. Data on the epidemiology of heart failure in Sub-Saharan Africa. Data Brief. 2018 Apr;17:1218-39.
10. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, et al. A new taxonomy for describing and defining adherence to medications. Br J Clin Pharmacol. 2012;73(5):691-705.
11. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376, 162 patients. Am J Med. 2012;125(9):882-7.
12. Marin MJ, Fábregues G, Rodríguez PD, Díaz M, Paez O, Alfie J, et al. National Registry of Hypertension. Awareness, Treatment and Control of Hypertension. The RENATA Study. Rev. Argent. Cardiol. 2012;80(2):121-8.
13. Corrao G, Parodi A, Nicotra F, Zambon A, Merlino L, Cesana G, et al. Better compliance to antihypertensive medications reduces cardiovascular risk. J Hypertens. 2011;29(3):610-8.
14. Morisky DE, Ang A, Krousel-Wood M, Ward HJ. Predictive validity of a medication adherence for hypertension control. J Hypertens. 2008;10(5):348-54.
15. C Carbajal HA. Optimal blood pressure and high normal blood pressure in La Plata, Argentina. Can J Cardiol. 1994;10(7):749-52.
16. Carey RM, Muntner P, Bosworth HB, Whelton PK. Prevention and Control of Hypertension: JACC Health Promotion Series. J Am Coll Cardiol. 2018;72(11):1278-93.
17. Hyre AD, Krousel-Wood MA, Muntner P, Kawasaki L, DeSalvo KB. Prevalence and predictors of poor antihypertensive medication adherence in an urban health clinic setting. J Clin Hypertens. 2007;9(3):179-86.
18. Hamdidouche I, Jullien V, Boutouyrie P, Billaud E, Azizi M, Laurent S. Routine urinary detection of antihypertensive drugs for systematic evaluation of adherence to treatment in hypertensive patients. J Hypertens. 2017;35(9):1891-8.
19. Calderón-Larrañaga A, Diaz E, Poblador-Plou B, Gimeno-Feliu LA, Abad-Díez JM, Prados-Torres A. Non-adherence to antihypertensive medication: the role of mental and physical comorbidity. Int J Cardiol. 2016 Mar 15;207:310-16.
20. Gentil L, Vasiliadis HM, Preville M, Bossé C, Berbiche D. Association between depressive and anxiety disorders and adherence to antihypertensive medication in community-living elderly adults. J Am Geriatr Soc. 2012;60(12):2297-301.
21. Holt E, Joyce C, Dornelles A, Morisky D, Webber LS, Muntner P, et al. Sex differences in barriers to antihypertensive medication adherence: findings from the cohort study of medication adherence among older adults. J Am Geriatr Soc. 2013;61(4):558-64.
22. Holt EW, Muntner P, Joyce CJ, Webber L, Krousel-Wood MA. Health-related quality of life and antihypertensive medication adherence among older adults. Age Ageing. 2010;39(4):481-7.
23. Ingaramo RA, Vita N, Bendersky M, Arnolt M, Bellindo C, Piscorz D, et al. Estudio Nacional Sobre Adherencia al Tratamiento (ENSAT).Rev Fed Arg Cardiol. 2005;34(1):104-11.

VIEWPOINT

PARAGON-HF: Lessons Learned and Perspectives

José Francisco Kerr Saraiva[1] and Isadora de Oliveira[2,3]

PUC-Campinas,[1] Campinas, SP – Brazil
Novartis Brasil - Medical Affairs,[2] São Paulo, SP – Brazil
Universidade de São Paulo,[3] São Paulo, SP – Brazil

An estimated 6.5 million Americans aged 20 and over have heart failure (HF) and projections show that the prevalence of HF will increase by 46% from 2012 to 2030, resulting in over 8 million people with HF.[1]

Patients with HF can be stratified into different categories of left ventricular ejection fraction (LVEF), presenting different phenotypes in terms of demographics, clinical presentation, etiology and outcomes. The current classification comprises HF with reduced ejection fraction (EF) [EF ≤ 40% (HFrEF)], with intermediate EF [EF 40-50% (HFiEF), and preserved EF [EF ≥ 50% (HFpEF).[2,3]

The diagnosis of HFpEF is challenging, starting with its definition and classification. The definition of HFpEF has evolved over the past two decades, from a primary focus on an echocardiographic evidence of diastolic dysfunction in the LVEF ≥ 50%, moving towards a definition that includes (but is not limited to) cardiac structural abnormalities resulting from high filling pressures, diastolic abnormalities, high levels of biomarkers and high left ventricular (LV) filling pressures.[2,3]

The risk of HFpEF increases with age. Additional risk factors for the development of HFpEF include hypertension, obesity, and coronary artery disease. HFpEF and atrial fibrillation (AF) are age-related conditions that commonly coexist and share clinical features. At least one third of patients with HFpEF have AF. Therefore, the prevalence of HfpEF has increased with increasing age and epidemics of obesity, hypertension and diabetes.[2,3]

Keywords

Heart Failure/physiopathology; Neprilysin/therapeutic use; Echocardiography/methods; Dysfunction Left Ventricular/abnormalities; Indicators of Morbidity and Mortality; Risk Factors; Valsartan/therapeutic use.

HFpEF is associated with high morbidity and mortality.[4] The survival of HFpEF is poor, particularly after hospitalization for HF. In a previous HFpEF epidemiology study, the survival of patients with HFpEF was 35% at 5 years after hospitalization for HF.[5]

The prevalence of HFpEF ranges from 31% to 55%. Female gender is an important risk factor for the development of HfpEF, and the reason for this is not clear. However, women may have greater arterial and ventricular stiffness, which can be exacerbated with age. In addition, reproductive hormones may influence LV structure and function and on the response to overload changes.[6]

Another point to stress is that HFpEF is underdiagnosed in the general population. Differently from HFrEF where most of patients are diagnosed, in HFpEF there is a window of opportunities to improve clinical recognition and diagnosis. Recently, the H_2FPEF, a score based on simple clinical and echocardiographic features to estimate the likelihood of HFpEF among patients with unexplained dyspnea, has been developed. This score includes the following variables: obesity (2 points), ≥ 2 antihypertensives (1 point), atrial fibrillation (3 points), pulmonary artery echocardiographic systolic pressure > 35 mm Hg (1 point), age ≥ 60 years (1 point) and echocardiogram E / e' > 9 (1 point).[7]

HFpEF, in addition to being a syndrome consisting of small left ventricle, significant concentric LV hypertrophy, normal EF, and diastolic dysfunction with reduced LV diastolic compliance, it is a multiorgan disease that involves not only the heart, but also the lungs, skeletal muscle, kidneys and adipose tissue.[8]

The pathophysiology of HFpEF is associated with systemic inflammation with subsequent reductions in biological functions of NO (nitric oxide), cyclic guanosine

Mailing Address: José Francisco Kerr Saraiva
Rua Oswaldo Oscar Barthelson, 1209 – Jardim Pauliceia. Postal Code: 13060-080, Campinas, SP – Brazil.
E-mail: jfsaraiva@uol.com.br

DOI: https://doi.org/10.36660/ijcs.20190222

Manuscript received on December 09, 2019; reviewed on December 11, 2019; accepted on December 30, 2019.

monophosphate (cGMP) content, and protein activity associated with cardiomyocyte hypertrophy, as well as decreased titin protein phosphorylation, which increases passive stiffness.[7]

With respect to treatment, there is no specific treatment to reduce mortality associated with HFpEF. Despite the availability of multiple therapies to modify the prognosis in patients with reduced LVEF, to this day, no therapy has proven to reduce morbidity and mortality for patients with LVEF (≥ 40%).

HFpEF has been defined as a heterogeneous disease. For the past 20 years, no clinical trials involving therapeutic strategies focused on neurohormonal modulation (which have been proven successful in HFrEF patients) have been able to show clinical benefit for HFpEF patients. Drugs like irbesartan, perindopril, spironolactone and candesartan have failed to show statistically significant benefit compared with placebo.[9-13]

Possible explanations for the inaccurate diagnosis of HFpEF include the fact that the pathophysiology is not completely understood (with wrong mechanisms of action), non-optimal inclusion criteria or outcomes in the studies, geographical variations in the diagnosis and treatment of HFpEF, and type and frequency of comorbidities. The most probable hypothesis is that we have been treating a syndrome and not a disease anymore, and in fact, this syndrome is made up of a heterogeneous group of related diseases that may not respond to a single treatment approach.

Symptomatic treatment of HFpEF is empirical and consists mainly of diuretics used to reduce congestion, although there isn't enough data to support their use. Similarly, data about heart rate control in patients with atrial fibrillation, which is highly prevalent in HFpEF, are also limited. It is not yet clear whether rhythm control would be beneficial in patients with HFpEF and atrial fibrillation.[14]

Yet these trials have not evaluated the effect of neprilysin inhibition, and the beneficial cardiovascular effects of natriuretic peptides in this population. The angiotensin receptor–neprilysin inhibitor sacubitril/valsartan resulted in a lower rate of hospitalization for HF or death from cardiovascular causes compared with enalapril among patients with HF and reduced LVEF (≤ 40%) in the PARADIGM-HF trial.[15] As for patients with HFpEF, sacubitril/valsartan resulted in a lower level of N-terminal pro–B-type natriuretic peptide, a larger reduction in left atrial size, and greater improvement in the NYHA functional class than valsartan in a phase II, randomized, placebo controlled clinical trial.[16]

The results of these two previous clinical trials provided the rational for the PARAGON-HF trial design. This was a phase III randomized, placebo controlled, event-driven trial designed to evaluate the safety and efficacy of sacubitril/valsartan compared to valsartan alone in patients with HF and preserved LVEF (≥ 45%).[17] The primary composite outcome of total hospitalizations for HF and death from cardiovascular causes did not differ significantly between the two groups. There were 894 primary events (690 hospitalizations for HF and 204 deaths from cardiovascular causes) in 526 patients in the sacubitril–valsartan group and 1,009 primary events (797 hospitalizations for HF and 212 deaths from cardiovascular causes) in 557 patients in the valsartan group (rate ratio, 0.87; 1 95% confidence interval [CI], 0.75 to 1.01; p = 0.06).[18] Despite the results for the primary endpoint, the PARAGON-HF was a step closer to understanding HFpEF. Of the 12 prespecified subgroups, two showed possible heterogeneity of treatment effect. The findings suggested beneficial effects in patients with an EF lower than the median (57%), and in women, who represented 52% of patients included in the final analysis. It is worth pointing out that the size of both subgroups was large enough for analysis (half the population in each subgroup).[18]

A secondary analysis of the PARAGON-HF has been recently published,[19] revealing that, compared with valsartan, sacubitril/valsartan reduced the risk of HF hospitalization more in women than in men. On the primary outcome (total HF hospitalizations and cardiovascular death), there was a more favorable treatment effect in women than in men (rate ratio 0.73 [0.59-0.90] in women; 1.03 [0.84-1.25] in men; p interaction = 0.017). Further analysis presented in this publication showed that this difference in effect was not explained by differences in the KCCQ questionnaire, NYHA class or renal outcomes.[19]

Another recent publication was a pre-specified pooled analysis of 13,195 patients from PARADIGM-HF (LVEF ≤ 40%; n = 8,399) and PARAGON-HF (LVEF ≥ 45%; n = 4,796), two similarly designed pivotal clinical trials. Pooled data enabled an analysis of treatment effect across the continuum of LVEF.

Among the findings, rates of primary composite events decreased with increasing LVEF, with lower rates of cardiovascular death, mainly in patients with the highest LVEF compared with patients with the lower

values. In addition, the therapeutic effects of sacubitril/valsartan, compared with a renin-angiotensin system (RAS) inhibitor alone, vary across the continuum of LVEF, with the greatest benefits, especially for HF hospitalization, observed in patients with a LVEF below approximately 60%. Therapeutic benefits of sacubitril/valsartan with respect to HF hospitalization and cardiovascular death are robust among patients with HFrEF; the PARAGON-HF data suggest that this benefit could be extended to patients with EF not frankly reduced (LVEF ≤ 55-60%).

The treatment effect across the EF continuum was also observed in the CHARM clinical program. As in PARAGON-HF, there was a potential benefit in favor of candesartan versus placebo in patients with an EF lower than 53%.[20] This effect was also observed in a TOPCAT post-hoc analysis.[21] Again, these data enhance the understanding of HFpEF but also raise questions about how we have been interpreting and diagnosing HF, and whether a broader range of patients (e.g., LVEF < 35%) could benefit from neurohormonal modulation. Despite this, there are no conclusive definitions on mid-range EF, where there probably be already disease progression and contractile impairment.

The PARAGON-HF is part of the sacubitril/valsartan clinical development program and provide us with another piece in the puzzle of neprilisin/ RAS inhibition in the complex scenario of HF syndrome. The study includes the assessment of the safety and efficacy of sacubitril/valsartan in different scenarios of HF including recently decompensated patients, across the spectrum of HF ejection fraction, pediatric HF patients and Chagas cardiomyopathy.

In addition, the PARALLAX-HF trial[22] will include patients with a LVEF ≥ 40% and complete the EF continuum analysis. Soon expected is the PARADISE-MI trial,[23] that will evaluate the safety and efficacy of sacubitril/valsartan versus ramipril in patients who have recently suffered a myocardial infarction. The study volunteers will not necessarily have a LVEF < 40%, as long as they have signs of pulmonary congestion requiring intravenous treatment with diuretics, vasodilators, vasopressors and/or inotropes, during the index hospitalization.[23] These new trials will bring new perspectives and possible therapeuthic options for patients with cardiovascular diseases associated with high morbidity and mortality .

Author contributions

Conception and design of the research: JFK Saraiva. Writing of the manuscript: JFK Saraiva, Oliveira IBD.

Potential Conflict of Interest

José Francisco Saraivais investigator in clinical trials mentioned in the paper. Isadora de Oliveira is medical affairs role in a company that may direct or indirectly benefit from this publication.

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. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017;14(10):591-602.
2. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2016;18(8):891-975.
3. Comitê Coordenador da Diretriz de Insuficiência Cardíaca; Rohde LEP, Montera MW, Bocchi EA, Clausell NO, Albuquerque DC de, Rassi S, et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. Arq Bras Cardiol .111(3):436-539.
4. Lam CSP, Gamble GD, Ling LH, Sim D, Leong KTG, Yeo PSD, et al. Mortality associated with heart failure with preserved vs. reduced ejection fraction in a prospective international multi-ethnic cohort study. Eur Heart J. 2018;39(20):1770-80.
5. Owan TE, Hodge DO, Herges RM, Jacobsen SJ, Roger VL, Redfield MM. Trends in Prevalence and Outcome of Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2006;355(3):251–9.
6. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med. 2015;175(6):996-1004.

7. Reddy YNV, Carter RE, Obokata M, Redfield MM, Borlaug BA. A Simple, Evidence-Based Approach to Help Guide Diagnosis of Heart Failure With Preserved Ejection Fraction. Circulation. 2018;138(9):861–70.

8. Lam CSP, Voors AA, de Boer RA, Solomon SD, van Veldhuisen DJ. Heart failure with preserved ejection fraction: from mechanisms to therapies. Eur Heart J. 2018;39(30):2780-92.

9. Shah SJ, Kitzman DW, Borlaug BA, van Heerebeek L, Zile MR, Kass DA, et al. Phenotype-Specific Treatment of Heart Failure With Preserved Ejection Fraction: A Multiorgan Roadmap. Circulation. 2016;134(1):73-90.

10. Pitt B, Pfeffer MA, Assmann SF, Boineau R, Anand IS, Claggett B, et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med. 2014;370(15):1383-92.

11. Yusuf S, Pfeffer MA, Swedberg K, Granger CB, Held P, McMurray JJ, et al. Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction: the CHARM-Preserved Trial. Lancet. 2003;;362(9386):777-81.

12. Massie BM, Carson PE, McMurray JJ, Komajda M, McKelvie R, Zile MR, et al. Irbesartan in patients with heart failure and preserved ejection fraction. N Engl J Med. 2008;359(23):2456-67.

13. Cleland JG, Tendera M, Adamus J, Freemantle N, Polonski L, Taylor J. The perindopril in elderly people with chronic heart failure (PEP-CHF) study. Eur Heart J. 2006;27(19):2338-45.

14. Kotecha D, Lam CSP, Van Veldhuisen DJ, Van Gelder IC, Voors AA, Rienstra M. Heart Failure With Preserved Ejection Fraction and Atrial Fibrillation. J Am Coll Cardiol. 2016 Nov;68(20):2217–28.

15. McMurray JJ, Packer M, Desai AS, Gong J, Lefkowitz MP, Rizkala AR, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014;371(11):993-1004.

16. Solomon SD, Zile M, Pieske B, Voors A, Shah A, Kraigher-Krainer E, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet. 2012;380(9851):1387-95.

17. Solomon SD, Rizkala AR, Lefkowitz MP, Shi VC, Gong J, Anavekar N, et al. Baseline Characteristics of Patients With Heart Failure and Preserved Ejection Fraction in the PARAGON-HF Trial. Circ Heart Fail.. 2018;11(7):e004962.

18. Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, et al. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. N Engl J Med. 2019;381(17):1609-20.

19. McMurray JJV, Jackson AM, Lam CSP, Redfield MM, Anand IS, Ge J, et al. Effects of Sacubitril-Valsartan, versus Valsartan, in Women Compared to Men with Heart Failure and Preserved Ejection Fraction: Insights from PARAGON-HF. Circulation. 2019 Nov 17;[Epub ahead of print].

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

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

22. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier NCT03066804, A Randomized, Double-blind Controlled Study Comparing LCZ696 to Medical Therapy for Comorbidities in HFpEF Patients (PARALLAX) [cited 2019 Dec 06]. Available from: https://clinicaltrials.gov/ct2/show/NCT03066804?id=NCT03066804&draw=2&rank=1&load=cart.

23. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). Identifier: NCT02924727, Prospective ARNI vs ACE Inhibitor Trial to DetermIne Superiority in Reducing Heart Failure Events After MI (PARADISE-MI) [cited 2019 Dec 06]. Available from: https://clinicaltrials.gov/ct2/show/NCT02924727?term=PARADISE-MI&draw=2&rank=1.

VIEWPOINT

Coronavirus Disease (COVID-19) Pandemic: An Opportunity Window to Implement Home-Based Cardiac Rehabilitation

Renata Rodrigues Teixeira de Castro

Faculdade de Medicina, Universidade Iguaçu, Nova Iguaçu, RJ - Brazil
Clínica de Cardiologia, Hospital Naval Marcílio Dias, Rio de Janeiro, RJ - Brazil
Cardiologia do Esporte, Rio de Janeiro, RJ - Brazil

The World Health Organization declared that the new coronavirus outbreak is a public health emergency of pandemic proportions. The outbreak has caused various governments to take protective measures such as lockdown of cities, travel bans, prohibition of group gatherings and public events, and social distancing. Many health and exercise training facilities were closed, as well as cardiac rehabilitation services. These restrictions are disrupting people's daily activities.

Although staying at home can contain virus spread, it will certainly reduce regular physical activity and increase sedentary behavior, which can increase the risk of development and worsening of chronic conditions.[1-7] Therefore, there is a strong evidence for continuing physical activity at home even during the pandemic situation.

Cardiac rehabilitation should be an integral component in the continuum of care for patients with cardiovascular disease.[8-12] Nevertheless, only a small number of patients that would benefit from cardiac rehabilitation is referred to the program. In the United Kingdom less than 20% of patients discharged with a diagnosis of heart failure are referred to cardiac rehabilitation.[13] In the United States, patient participation in cardiac rehabilitation is also low, with only 16.3% of Medicare patients and 10.3% of veterans after hospital discharge for myocardial infarction, percutaneous coronary intervention or coronary artery bypass graft surgery.[14] In Brazil, access to cardiac rehabilitation programs is also suboptimal.[15]

There is an urgent need for new cardiac rehabilitation strategies that overcome current geographical, logistical, cost-related and access-related barrier.[13,16] Although training at home is usually recommended when training at cardiac rehabilitation facility is not possible, few physicians feel confident prescribing stand-alone exercises to cardiac patients. Nevertheless, the European Guidelines on Cardiovascular disease prevention states that "home-based rehabilitation with and without telemonitoring holds promise for increasing participation and supporting behavioral change".[17] Noteworthy, Cochrane reviews[18-20] concluded that home-based cardiac rehabilitation and traditional cardiac rehabilitation programs have similar effects on quality of life of patients with recent myocardial infarction or coronary revascularization.

The American College of Cardiology, the American Heart Association and the American Association of Cardiovascular and Pulmonary Rehabilitation have recently published a scientific statement on home-based cardiac rehabilitation.[16] In this document, cardiac rehabilitation interventions should include exercise training, dietary education, medication management, tobacco counseling and psychosocial assessment.

It is important to note that proper patient evaluation at baseline is critical to correctly prescribe these interventions. Although cardiopulmonary exercise testing and physical examination cannot be performed remotely, telemedicine may offer the possibility of history taking.[21] We must consider that, for patients already participating in formal cardiac

Keywords

Coronavirus/isolation & purification; Coronavirus Infections/prevention and control; Syndrome Acute Respiratory; Cardiovascular Diseases; Hypertension; Diabetes; Comorbidity; Physical Activity; Exercise; Cardiac Rehabilitation; Public Health Services.

Mailing Address: Renata Rodrigues Teixeira de Castro
Rua Prudente de Morais, 1788. Ipanema, Rio de Janeiro, RJ - Brazil
E-mail: castrorrt@gmail.com

DOI: https://doi.org/10.36660/ijcs.20200062

Manuscript received on April 04, 2020, revised manuscript on April 07, 2020, accepted on April 07, 2020.

rehabilitation programs, exercise prescriptions will probably not need to be changed during the social distancing period.

Despite the fact that severe cardiovascular events are rare during cardiac rehabilitation trainings,[22] safety is a major concern in cardiac rehabilitation facilities and this should not be different in remote rehabilitation programs. Thus, in cases where social distance prevented proper patient evaluation and risk assessment, light-intensity exercise should be preferred and cardiac rehabilitation should focus on dietary education, medication management, tobacco counseling and psychosocial assessment that can be delivered remotely.

Therefore, current evidence suggests that remote cardiac rehabilitation programs must be implemented during the pandemic, since the risks of sedentary behavior outweigh the risks of well-planned programs.

Author contributions

Conception and design of the research; Acquisition od data; Analysis and interpretation of the data; Writing of the manuscrip; Critical revision of the manuscript for intellectual content: Castro RRT.

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 graduation program.

References

1. Chen P, Mao L, Nassis GP, Harmer P, Ainsworth BE, Li F. Coronavirus disease (COVID-19): The need to maintain regular physical activity while taking precautions. *J Sport Health Sci.* 2020;9(2):103-4.
2. Owen N, Sparling PB, Healy GN, Dunstan DW, Matthews CE. Sedentary behavior: emerging evidence for a new health risk. *Mayo Clin Proc.* 2010;85(12):1138-41.
3. Henson J, Dunstan DW, Davies MJ, Yates T. Sedentary behaviour as a new behavioural target in the prevention and treatment of type 2 diabetes. *Diabetes Metab Res Rev.* 2016;32(Suppl 1):213-20.
4. Hamilton MT, Healy GN, Dunstan DW, Zderic TW, Owen N. Too Little Exercise and Too Much Sitting: Inactivity Physiology and the Need for New Recommendations on Sedentary Behavior. *Curr Cardiovasc Risk Rep.* 2008;2(4):292-8.
5. Eanes L. CE: Too Much Sitting: A Newly Recognized Health Risk. *Am J Nurs.* 2018;118(9):26-34.
6. Ding D, Rogers K, van der Ploeg H, Stamatakis E, Bauman AE. Traditional and Emerging Lifestyle Risk Behaviors and All-Cause Mortality in Middle-Aged and Older Adults: Evidence from a Large Population-Based Australian Cohort. *PLoS Med.* 2015;12(12):e1001917.
7. Simpson RJ, Kunz H, Agha N, Graff R. Exercise and the Regulation of Immune Functions. *Prog Mol Biol Transl Sci.* 2015;135:355-80.
8. Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, et al. et al. Impact of Exercise Rehabilitation on Exercise Capacity and Quality-of-Life in Heart Failure: Individual Participant Meta-Analysis. *J Am Coll Cardiol.* 2019;73(12):1430-43.
9. Servey JT, Stephens M. Cardiac Rehabilitation: Improving Function and Reducing Risk. *Am Fam Physician.* 2016;94(1):37-43.
10. Piepoli MF, Corra U, Benzer W, Biarnason-Wehrens B, Dendale P, Gaita D, et al. Secondary prevention through cardiac rehabilitation: from knowledge to implementation. A position paper from the Cardiac Rehabilitation Section of the European Association of Cardiovascular Prevention and Rehabilitation. *Eur J Cardiovasc Prev Rehabil.* 2010;17(1):1-17.
11. Herdy AH, López-Jiménez F, Terzic CP,Milani M, Stein R, Carvalho T, et al. et al. South American guidelines for cardiovascular disease prevention and rehabilitation. *Arq Bras Cardiol.* 2014;103(2 Suppl 1):1-31.
12. Benzer W, Rauch B, Schmid JP, Bonner G, Ouarrak T, McGee H, et al. Exercise-based cardiac rehabilitation in twelve European countries results of the European cardiac rehabilitation registry. *Int J Cardiol.* 2017;228:58-67.
13. Dalal HM, Taylor RS, Doherty P. Home-based rehabilitation for heart failure: we need to act now. *Eur J Prev Cardiol.* 2019;26(12):1343-4.
14. Beatty AL, Truong M, Schopfer DW, Shen H, Bachmann JM, Whooley MA. Geographic Variation in Cardiac Rehabilitation Participation in Medicare and Veterans Affairs Populations: Opportunity for Improvement. *Circulation.* 2018;137(18):1899-908.
15. Britto RR, Supervia M, Turk-Adawi K, Chaves GS, Pesah E, Lopez-Jimenez F, et al. Cardiac rehabilitation availability and delivery in Brazil: a comparison to other upper middle-income countries. *Braz J Phys Ther.* 2020;24(2):167-76.
16. Thomas RJ, Beatty AL, Beckie TM, Brewer LC, Brown TM, Forman DE, et al. Home-Based Cardiac Rehabilitation: A Scientific Statement From the American Association of Cardiovascular and Pulmonary Rehabilitation, the American Heart Association, and the American College of Cardiology. *J Am Coll Cardiol.* 2019;74(1):133-53.
17. Piepoli MF, Hoes AW, Agewall S,Albus C, Brotons C, Catapano AL, et al.. [2016 European guidelines on cardiovascular disease prevention in clinical practice. The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts. Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation]. *G Ital Cardiol (Rome).* 2017;18(7):547-612.
18. Anderson L, Sharp GA, Norton RJ, Dalal H, Dean SG, Jolly K, et al. Home-based versus centre-based cardiac rehabilitation. *Cochrane Database Syst Rev.* 2017;6:CD007130.
19. Buckingham SA, Taylor RS, Jolly K, Zawada A, Dean SG, et al. Home-based versus centre-based cardiac rehabilitation: abridged Cochrane systematic review and meta-analysis. *Open Heart.* 2016;3(2):e000463.
20. Taylor RS, Dalal H, Jolly K, et al. Home-based versus centre-based cardiac rehabilitation. *Cochrane Database Syst Rev.* 2015(8):CD007130.
21. Tuckson RV, Edmunds M, Hodgkins ML. Telehealth. *N Engl J Med.* 2017;377(16):1585-92.
22. Haskell WL. The efficacy and safety of exercise programs in cardiac rehabilitation. *Med Sci Sports Exerc.* 1994;26(7):815-23.

VIEWPOINT

Exercise Training: A Hero that Can Fight two Pandemics at Once

Renata Rodrigues Teixeira de Castro,[1,2,3] João Giffoni da Silveira Neto,[1,3] Roberta Rodrigues Teixeira de Castro[1,3]

Universidade Iguaçu,[1] Nova Iguaçu, RJ – Brazil
Hospital Naval Marcílio Dias, Comando da Marinha,[2] Rio de Janeiro, RJ – Brazil
Cardiologia do Esporte,[3] Rio de Janeiro, RJ – Brazil

On March 11th, 2020, the World Health Organization (WHO) declared that the new COVID-19 outbreak was a public health emergency of pandemic proportions. At that time, there were more than 118,000 infected patients in 114 countries and 4,291 people had lost their lives. While daily statistics show increases in the number of deceased and infected people, and despite all the efforts of scientists all over the world, governments and healthcare professionals are facing the challenge of taking decisions driven on data that is new, incomplete or even unavailable.[1-3]

To prevent virus spreading, some governments put major cities in lockdown and others promoted social distancing, banning public events and shutting down public places, including parks and beaches. Gyms and other training facilities were also closed, leaving people with no secure place to exercise. At first glance, it may seem that there is no other option, but to stay home without exercising. Nevertheless, not exercising is not the only choice for people practicing social isolation. It is, in fact, a very unhealthy choice that should not be considered.

The sedentarism pandemic

The WHO recommends that adults aged 18 years and older should accumulate at least 150 minutes of moderate-intensity aerobic activity, 75 minutes of vigorous-intensity aerobic activity, or a combination of both per week.[4] People who do not meet these requirements are considered sedentary. The health benefits of physical exercise include lower risks of cardiovascular disease, hypertension, diabetes, obesity, dementia and breast and colon cancer.[5-9] Despite all these benefits, sedentarism is a pandemic, affecting 27.5% of people globally.[10]

Sedentarism increases the risk of the world´s major non-communicable diseases. I-Min Lee et al.,[11] estimated that physical inactivity is responsible for 6% of the burden of coronary artery disease, 7% of type 2 diabetes, 10% of breast cancer and colon cancers. Thus, inactivity is considered responsible for 9% of premature mortality, globally. Actually, sedentarism kills more people annually than the COVID-19 infection.

Comorbidities and prognosis in patients with COVID-19

Yang et al.,[12] described that, in Chinese patients infected with COVID-19, hypertension was the most prevalent comorbidity (17 ± 7%), followed by diabetes (8 ± 6%) and cardiovascular diseases (5 ± 4%). Another meta-analysis confirmed that these comorbidities were associated with poor prognosis. Data about exercise habits in patients infected by COVID-19 is yet not available. Nevertheless, it is clear that these comorbidities would be less prevalent if minimal WHO´s exercise requirements were globally met.[4]

Exercise training can help fight viral infections

Exercise training is considered effective in primary prevention and in the treatment of most chronic diseases,[11,13-16] especially the most prevalent ones, that confers worst prognosis in COVID infections. Thus, physical training itself may prevent deaths during this pandemic.

Keywords

COVID-19; Coronavirus, Communicable Diseases, Emerging; Pandemics; Exercise; Motor Activity/methods; Comorbidity; Social Isolation; Breathing Exercises/methods.

Mailing Address: Renata Rodrigues Teixeira de Castro
Rua Prudente de Morais, 1788. Ipanema, Rio de Janeiro, RJ - Brazil
E-mail: castrorrt@gmail.com

DOI: https://doi.org/10.36660/ijcs.20200083

Manuscript received on April 15, 2020, revised manuscript on April 24, 2020, accepted on April 25, 2020.

Physical training is also known to improve immune response. Despite the concerns of some athletes about the side effects of vaccination, high exercise intensity and frequency enhance vaccine-responses in elite athletes.[17] This is also true in older people where immunoglobulins concentrations after vaccinations are greater in cardiovascular-trained individuals than in control ones.[17-22]

Despite the promising effects of exercise training on the immune system, exercise stress may be associated with an increased risk for upper respiratory tract infection.[23] Acute bouts of heavy exercise and chronic intensive exercise, as usually performed by long-distance runners, compromise host defenses and increase the incidence of upper respiratory tract infections.[24,25] In athletes under heavy training both innate and acquired immunity are often observed to decrease, typically 15-25%.[26]

It is true that exercise can modulate many immune system components, altering the susceptibility to infections, which means that exercise training may increase or reduce the susceptibility to infections. Although it may seem paradoxical, this assertive is true, and quite straightforward. A large study[27] about the Hong Kong flu outbreak in 1998 concluded that mild to moderate exercise, performed three to five times per week reduced the risk of mortality, while people who did not exercise or who exercised too much were at greatest risk of death. Thus, the missing piece of the survival puzzle during pandemic is not exercise itself, but its detailed prescription.

Exercise prescription during the COVID pandemic

Physicians learn how to prescribe various drugs. Although exercise is beneficial for the treatment of several diseases, exercise prescription is not taught to medicine students or residents.[28,29] As any other medication, exercise training needs the right dosing to achieve the desired effects. The American College of Sports Medicine has introduced the FITT-VP principle as a mnemonic with all the points that must me described in exercise prescription: Frequency, Intensity, Type, Time, Volume and Progression.[6]

Social restrictions, correctly imposed during the COVID-19 pandemic, is certainly disrupting routine daily activities of people globally.[30] Still, there are exercises that can be safely done at home. Considering the previous discussion on the minimal training volume[4] for health, recommended by the WHO, and the embedded risks of immunity reduction due to high intensity training, the following principles can guide home-based exercise while at social isolation.

First do no harm

This principle of the Hippocratic Oath applies here. Exercise has its risks, which are not easily gathered remotely. Before starting exercising by themselves, patients must be sure that all questions in the PAR-Q questionnaire[31-33] are negative. In addition, it is not recommended to exercise if the patient is experiencing flu symptoms, sore throat, body aches, shortness of breath, fatigue cough or fever. Patients with any positive answer to the PAR-Q questionnaire or presenting any of these symptoms should seek medical advice before start exercising.

Frequency

Guidelines suggest that sedentary people start with aerobic exercise 3 to 5 times per week and that resistance training is done 2 to 3 times per week. Flexibility and mobility exercises can be done on most days.

Intensity

During the pandemics, one should not engage in high intensity exercise. That being said, it is important to know how to evaluate exercise intensity. There are various ways to do that, but some, such as anaerobic threshold, maximal oxygen volume uptake and real maximal heart rate, require exercise tests not available during the pandemic. Although the maximum heart rate calculation (Maximum heart rate=220 -age) presents errors,[34] it is probably the most feasible way to analyze one´s maximal heart rate when maximal exercise tests cannot be done.

During light intensity exercise, heart rate is kept below 45% of maximum heart rate. The heart rate during moderate intensity exercise is kept between 64 and 76% of maximum heart rate. Thus, during the pandemic, exercise heart rate should not be higher than 77% of maximum heart rate (vigorous exercise).

Resistance exercise prescription usually considers percentages of repetition maximum for each exercise.[6,35]. As repetition maximum tests uses equipment that are not available at home, some adaptations need to be done. Strength exercises that

only requires body weight, as pushups, sit-ups and lunges can be done. Resistance bands are also good options. If more resistance is needed, books, food packages and other objects can all be used as weights for training.

Time

Exercise duration depends on individual aerobic capacity, but sets of 30 to 50 minutes are recommended.

Type

Multicomponent exercise programs including aerobic, resistance, flexibility and balance training exercises are recommended[4].

Volume

Guidelines recommend at least 150 minutes of aerobic exercise and two resistance training sessions per week. My personal view, considering the risks of immune depletion related to high volume training, is that people who used to exercise before the pandemic should try to keep the same training volume. People who were sedentary should try to adhere to the minimal requirements.

Progression

It is time to keep fit, not to pursue increases in fitness.

Conclusion

Government measures that restrict people at home during the COVID-19 pandemic do not need to encourage the wider spread of the sedentarism pandemic. Exercise can fight both public health problems, as long as it is adequately prescribed. Maintaining regular physical activity at home is pivotal for healthy living during and after the COVID-19 global crisis.

Author contributions

Conception and design of the research: Castro RRT. Acquisition od data: Castro RRT. Analysis and interpretation of the data: Castro RRT. Writing of the manuscript: Castro RRT, Silveira Neto JG, Castro RRT. Critical revision of the manuscript for intellectual content: Castro RRT, Silveira Neto JG, Castro RRT.

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 graduation program.

References

1. Calisher C, Carroll D, Colwell R, Corley RB, Daszak P, Drosten C, et al. Statement in support of the scientists, public health professionals, and medical professionals of China combatting COVID-19. *Lancet.* 2020;395(10226):e42-e43.
2. Li H, Zhou Y, Zhang M, Wang H, Zhao Q, Liu J. Updated approaches against SARS-CoV-2. *Antimicrob Agents Chemother.* 2020.
3. Lippi G, Plebani M. The critical role of laboratory medicine during coronavirus disease 2019 (COVID-19) and other viral outbreaks. *Clin Chem Lab Med.* 2020.
4. World Health Organization. (WHO. Global recommendation on physical activity for health. Geneva: 2010.
5. Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation.* 2013;128(8):873-934.
6. Garber CE, Blissmer B, Deschenes MR, Franklin BA, Lamonte MJ, Lee IM, et al. American College of Sports Medicine position stand. Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy adults: guidance for prescribing exercise. *Med Sci Sports Exerc.* 2011;43(7):1334-59.
7. Sales AR, Silva BM, Neves FJ, Rocha NG, Medeiros RF, Castro RR, et al. Diet and exercise training reduce blood pressure and improve autonomic modulation in women with prehypertension. *Eur J Appl Physiol.* 2012;112(9):3369-78.
8. Taylor RS, Walker S, Smart NA, Piepoli MF, Warren FC, Ciani O, et al. Impact of Exercise Rehabilitation on Exercise Capacity and Quality-of-Life in Heart Failure: Individual Participant Meta-Analysis. *J Am Coll Cardiol.* 2019;73(12):1430-43.
9. Herdy AH, López-Jiménez F, Terzic CP, Milani M, Stein R, Carvalho T, et al. South American guidelines for cardiovascular disease prevention and rehabilitation. *Arq Bras Cardiol.* 2014;103(2 Suppl 1):1-31.
10. 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 Glob Health.* 2018;6(10):e1077-e1086.
11. I-Min L, Shiroma E, Lobelo F, Puska P, Blair S, Katzmarzyk P. Impact of Physical Inactivity on the World's Major Non-Communicable Diseases. *Lancet.* 2012;380:11.
12. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q, et al. Prevalence of comorbidities in the novel Wuhan coronavirus (COVID-19) infection: a systematic review and meta-analysis. *Int J Infect Dis.* 2020. [Epub ahead of print]
13. Blair SN, Kohl HW, Paffenbarger RS, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. *JAMA.* 1989;262(17):2395-401.
14. Lavie CJ, Ozemek C, Carbone S, Katzmarzyk PT, Blair SN. Sedentary Behavior, Exercise, and Cardiovascular Health. *Circ Res.* 2019;124(5):799-815.

15. Fletcher GF, Landolfo C, Niebauer J, Ozemek C, Arena R, Lavie CJ. Promoting Physical Activity and Exercise: JACC Health Promotion Series. *J Am Coll Cardiol.* 2018;72(14):1622-39.

16. Ozemek C, Laddu DR, Lavie CJ, Claeys H, Kaminsky LA, Ross R,et al. An Update on the Role of Cardiorespiratory Fitness, Structured Exercise and Lifestyle Physical Activity in Preventing Cardiovascular Disease and Health Risk. *Prog Cardiovasc Dis.* 2018;61(5-6):484-90.

17. Ledo A, Schub D, Ziller C, Enders M, Stenger T, Gärtner BC, et al. Elite athletes on regular training show more pronounced induction of vaccine-specific T-cells and antibodies after tetravalent influenza vaccination than controls. *Brain Behav Immun.* 2020;83:135-45.

18. Grant RW, Mariani RA, Vieira VJ, Fleshner M, Smith TP, Keylock KT, et al. Cardiovascular exercise intervention improves the primary antibody response to keyhole limpet hemocyanin (KLH) in previously sedentary older adults. *Brain Behav Immun.* 2008;22(6):923-32.

19. Schuler PB, Leblanc PA, Marzilli TS. Effect of physical activity on the production of specific antibody in response to the 1998-99 influenza virus vaccine in older adults. *J Sports Med Phys Fitness.* 2003;43(3):404.

20. de Araújo AL, Silva LC, Fernandes JR, Matias M de S, Boas LS, Machado CM, et al. Elderly men with moderate and intense training lifestyle present sustained higher antibody responses to influenza vaccine. *Age (Dordr).* 2015;37(6):105.

21. Simpson RJ, Kunz H, Agha N, Graff R. Exercise and the Regulation of Immune Functions. *Prog Mol Biol Transl Sci.* 2015;135:355-80.

22. Smith TP, Kennedy SL, Fleshner M. Influence of age and physical activity on the primary in vivo antibody and T cell-mediated responses in men. *J Appl Physiol.1985; (1985).* 2004;97(2):491-8.

23. Murphy EA, Davis JM, Carmichael MD, Gangemi JD, Ghaffar A, Mayer EP. Exercise stress increases susceptibility to influenza infection. *Brain Behav Immun.* 2008;22(8):1152-5.

24. Peters EM, Bateman ED. Ultramarathon running and upper respiratory tract infections. An epidemiological survey. *S Afr Med J.* 1983;64(15):582-4.

25. Nieman DC, Johanssen LM, Lee JW, Arabatzis K. Infectious episodes in runners before and after the Los Angeles Marathon. *J Sports Med Phys Fitness.* 1990;30(3):316-28.

26. Walsh NP, Oliver SJ. Exercise, immune function and respiratory infection: An update on the influence of training and environmental stress. *Immunol Cell Biol.* 2016;94(2):132-9.

27. Wong CM, Lai HK, Ou CQ, Ho SY, Chan KP, Thach TQ, et al. Is exercise protective against influenza-associated mortality? *PLoS One.* 2008;3(5):e2108.

28. Solmundson K, Koehle M, McKenzie D. Are we adequately preparing the next generation of physicians to prescribe exercise as prevention and treatment? Residents express the desire for more training in exercise prescription. *Can Med Educ J.* 2016;7(2):e79-e96.

29. Windt J, Windt A, Davis J, Petrella R, Khan K. Can a 3-hour educational workshop and the provision of practical tools encourage family physicians to prescribe physical activity as medicine? A pre-post study. *BMJ Open.* 2015;5(7):e007920.

30. Chen P, Mao L, Nassis GP, Harmer P, Ainsworth BE, Li F. Coronavirus disease (COVID-19): The need to maintain regular physical activity while taking precautions. *J Sport Health Sci.* 2020;9(2):103-4.

31. Shephard RJ, Cox MH, Simper K. An analysis of "Par-Q" responses in an office population. *Can J Public Health.* 1981;72(1):37-40.

32. Shephard RJ. PAR-Q, Canadian Home Fitness Test and exercise screening alternatives. *Sports Med.* 1988;5(3):185-95.

33. Thomas S, Reading J, Shephard RJ. Revision of the Physical Activity Readiness Questionnaire (PAR-Q). *Can J Sport Sci.* 1992;17(4):338-45.

34. RA R, R L. The surprising history of the "HRmax=220-age"equation. *Journal of Exerc Physiol.* 2002;5(2):10.

35. Medicine ACoS. American College of Sports Medicine position stand. Progression models in resistance training for healthy adults. *Med Sci Sports Exerc.* 2009;41(3):687-708.

VIEWPOINT

Covid-19 and Safety in the Cath Lab: Where We Are and Where We Are Headed

Giordana Zeferino Mariano,[1] Viviana Guzzo Lemke,[2] Maria Sanali Moura Paiva,[3] Gláucia Maria Moraes de Oliveira[4]

Hospital São João Batista,[1] Criciúma, SC – Brazil
Hospital das Nações, Curitiba,[2] PR – Brazil
Universidade Federal do Rio Grande do Norte (UFRN),[3] Natal, RN – Brazil
Universidade Federal do Rio de Janeiro (UFRJ),[4] Rio de Janeiro, RJ – Brazil

The COVID-19 pandemic, caused by the betacoronavirus SARS-CoV-2, has rapidly spread worldwide from the city of Wuhan, China. Since its beginning, it has affected more than 2,700,000 individuals and caused almost 185,000 deaths in 185 countries, compounding the difficulties in medical healthcare worldwide. By April 23, 2020, Brazil had registered almost 47,000 confirmed cases and 3,000 deaths.[1]

COVID-19 aggravates the inequalities and uncertainties of science in general. This is no different when it comes to the heart. Unlike other epidemics caused by respiratory viruses, COVID-19 affects the heart, not only because most confirmed cases and deaths involve individuals with hypertension, heart failure, arrhythmias and coronary artery disease, but also because the disease is associated with a higher number of cardiac complications, such as myocardial injury, cardiogenic shock, Takotsubo syndrome, pulmonary embolism, myocarditis and arrhythmia.[2] Apart from inflammation, endothelial activation, oxidation of low-density lipoproteins, platelet activation and tissue factor expression caused by respiratory virus epidemics, such as severe acute respiratory syndrome (SARS) and Middle-East respiratory syndrome (MERS), poor COVID-19 prognosis is compounded by the deleterious effect of the association of treatment drugs (chloroquine/azithromycin) that can cause malignant arrhythmias in patients with heart disease.[3]

Keywords

Coronavirus; COVID-19; Pandemics; Pathological Conditions, Signs and Symptoms; Fever; Cough; Dyspnea; Fatigue; Diarrhea; Chest Pain; Mental Confusion; Myalgia, Cardiovascular Diseases/complications; Safety.

The challenges concerning COVID-19 are huge, because it tests us all - patients, healthcare personnel, health systems and the general population. In light of this, the importance of the safety of healthcare workers has never been so emphasized.[2]

Working in a hospital during a pandemic of a highly contagious disease, such as COVID-19, reminds healthcare workers of the need to reinforce all safety measures inside a cardiac catheterization laboratory (CCL). That is because, in addition to the cardiovascular alterations due to COVID-19, patients with cardiovascular diseases, such as acute myocardial infarction and advanced structural diseases, continue to require interventional procedures.

Therefore, the safety measures for healthcare professionals and patients become even more important during the COVID-19 pandemic. Some of the safety issues that might affect both patients and healthcare personnel are as follows: ionizing radiation, equipment, and contact with chemical and biological agents. All health professionals in contact with patients should follow the local and national guidelines for infection control and use of personal protective equipment (PPE), which should be available and on hand for all staff members. In addition, strict adherence to all safety rules required for a catheterization procedure indication should be encouraged; moreover, all urgent cases should be prioritized, and all routine cases postponed if this carries no loss to either prognosis or the patients' quality of life.[4]

The Brazilian Society of Interventional Cardiology (SBHCI) has published a position statement on some general measures to tackle COVID-19: limitation of social exposure; adoption of stricter personal hygiene habits; home confinement of individuals with the mild

Mailing Address: Gláucia Maria Moraes de Oliveira
Universidade Federal do Rio de Janeiro – R. Prof. Rodolpho P. Rocco, 255 – Prédio do HU 8º 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.20200080

Manuscript received April 23, 2020; revised manuscript April 25, 2020; accepted April 26, 2020.

form of COVID-19; hospital support with isolation for patients with the severe forms of the disease; quarantine for the close contacts of suspected cases; priority allocation of healthcare resources to urgent and emergent cases; protection of the professionals involved in patients' care. In addition, regarding specifically the CCL, the SBHCI recommends: to postpone elective procedures in patients with confirmed or suspected COVID-19; to limit the performance of CCL procedures to cardiovascular emergencies, and, for the other cases, procedures must be postponed until the non-infecting stage of disease; in CCLs with multiple procedure rooms, one should be dedicated to the treatment of suspected or confirmed COVID-19 patients.[5]

During the COVID-19 pandemic, the general safety protocols and those concerning CCL procedures, as well as the safety measures for patients and healthcare personnel need to be reviewed, because that infection increases the requirements for indication and effectiveness of the procedures performed.

Safety measures in the procedure preparation stage

A study conducted in China with 72,314 patients with COVID-19 (44,672 laboratory-confirmed cases, 16,186 suspected cases, and 10,567 clinically diagnosed cases) has reported fever, cough, dyspnea, myalgia, fatigue and diarrhea as the most common symptoms. Other signs and symptoms have been reported, such as sore throat, chest pain, mental confusion, and lethargy. The authors have highlighted that COVID-19 had a benign course in 80% of the cases, and that many patients, although asymptomatic, could carry the virus.[6] It is worth noting the importance of the differential diagnosis of dyspnea and fatigue, especially when associated with the other symptoms.

During a respiratory pandemic, patients and their families should be informed about the risks of contamination, despite all additional measures taken to minimize them. Because the number of elective procedures will be drastically reduced during that period, the length of hospital stay is predicted to be the minimum necessary for each protocol consensually elaborated.[7] Moreover, defining a procedure as elective requires clinical judgement, because postponing it might have effects that will increase the likelihood of decompensation and adverse events during the pandemic, such as in high-risk patients with unstable angina. Therefore, the decision about performing a procedure should be individualized and based on the patient's risk and benefit analysis.[8]

Despite the adoption of measures to reduce exposure, healthcare personnel shortage should be anticipated based on the likelihood of the removal of infected, exposed, at-risk and quarantined healthcare personnel. Particular attention should be given to avoid simultaneous exposure of healthcare professionals sharing the same skill set to prevent simultaneous contamination, especially in teaching institutions where the staff usually act together.[4] In addition, it is worth emphasizing the importance of reducing as much as possible the circulation in the procedure room to ensure the minimum safety threshold established in CCL procedural protocols.[4]

It is worth noting that patients with suspected or confirmed COVID-19 should ideally undergo procedures at the end of the day or in CCL rooms dedicated to COVID-19, when available, because of the need for terminal disinfection.[4]

Patients already intubated represent a lower risk of contamination to healthcare personnel, because they are on closed-loop ventilation. In patients with suspected or confirmed COVID-19 who need orotracheal intubation, this intervention should be performed before arrival to the CCL; in addition, intubation should be considered as early as possible in borderline patients to avoid the need for an urgent procedure and to minimize the contamination of the staff.[4]

Safety measures concerning the procedures

Healthcare personnel exposure and benefits to patients should be balanced for all interventional procedures. For example, during a respiratory epidemic, for hemodynamically stable patients with COVID19+ and ST-segment elevation myocardial infarction, fibrinolysis might be an alternative according to some authors;[6,9] however, the length of hospital stay waiting for coronary angioplasty after fibrinolysis should be carefully considered.

It is worth noting that COVID19 is spread via respiratory droplets and contact with surfaces on which the virus can last for long periods, such as cell phone, keyboard, mouse and door handles, thus, the procedure duration should be reduced to a minimum.[10,11] Moreover, patients with suspected or confirmed COVID-19 should be using a face mask upon arrival to the CCL and continue to use it during procedure preparation and the procedure itself.[4]

All CCL personnel should wear PPE, including FFP2/N95 respirators, goggles, full face shields, disposable caps, gowns, surgical gloves, and shoe covers, during the entire procedure, because of the potential for those patients' clinical deterioration and the consequent risk that comes with intubation, aspiration and cardiopulmonary resuscitation. In addition, CCL staff should be well educated in the proper donning and doffing of PPE because of the high likelihood of contamination involved in the process.[3-5]

It is worth noting that myocardial injury has been reported in 7% of the patients with COVID-19 and might correspond to type 2 myocardial infarction or myocarditis.[11] Thus, no effort should be spared in reaching the differential diagnosis before the procedure with the aid of imaging tests, such as point-of-care echocardiography.

In addition, it is worth emphasizing that percutaneous coronary intervention should only be performed to the culprit vessel, unless a nonculprit lesion is deemed unstable or in the presence of multiple culprit lesions.[12]

Post-procedure safety measures

During the pandemic, in anticipation of a surge in hospitalization required for COVID-19 infected patients and because not only most inpatient beds will be made available for COVID-19 treatment, but also to avoid additional contamination, hospital discharge will occur earlier for stable patients who might be followed up via telemedicine.[12]

Within the CCL, all nonessential equipment should be moved out of the procedure room or covered with clear drapes before patient's arrival to the room, and the same applies to the control and post-procedure recovery rooms. After a procedure in a patient with COVID-19, thorough terminal disinfection can be performed with ultraviolet light.[12]

The standard positive pressure ventilation system of the CCL consists of an air-handling unit that distributes conditioned air to different functional units, including the procedure, post-procedure, and control rooms. Positive pressure with adequate air changes can rapidly eliminate the virus from the environment; in addition the risk of cross-contamination from airborne infections has been shown to be low if the personnel is protected with appropriate PPE.[9] The positive pressure ventilation system should be extended to the rooms associated with the procedure.

It is worth noting that the inflammatory state of patients with COVID-19 often determines a hypercoagulable condition that requires additional use of heparin.[11]

Figure 1 shows the safety recommendations for CCL procedures during the COVID-19 pandemic. Those written in bold letters should receive special attention during the COVID-19 pandemic.

Safety and protective measures for healthcare workers

During the COVID-19 pandemic, all material used for invasive procedures, including the equipment for anesthesia, orotracheal intubation and mechanical ventilation, in addition to PPEs, should undergo a daily check and be readily available for easy and rapid use to minimize the work and burnout of healthcare professionals.[13]

The PPE should be removed preferably in an anteroom. If no anteroom is available, doffing of PPE should be done inside the procedure room, at the end of the procedure and after the patient has been transferred away, except for the PPE for respiratory protection, which must be removed outside the procedure room.[13]

Post-procedure visits should be performed by the lowest number possible of professionals; moreover, discussions about additional management should be converted to an online or telephone format, and the same applies to morning CCL rounds.[12-14]

Most sanitizers contain alcohol at different concentrations and are used for cleaning and disinfecting high-touch surfaces (floor, walls, ceiling, and countertops), a precaution that is important during the COVID-19 pandemic. SARS-CoV-2, a single-strand RNA virus, is sensitive to ultraviolet radiation and heat, being inactivated by lipid solvents, such as ether (75%), ethanol, sanitizers containing chlorine, peroxyacetic acid and chloroform, except for chlorhexidine.[15]

Terminal disinfection of the procedure room at the end of each procedure is highly recommended during the COVID-19 pandemic. Disposable PPE, sheets, fabric, and sponges contaminated with blood should be placed into a waste container marked with the biological hazard symbol and disposed into a waste bin labeled as 'COVID-19'.[10]

Figure 2 shows the general safety items for CCL procedures. Those written in bold letters should receive special attention during the COVID-19 pandemic.

Figure 3 shows the steps for putting on and removing PPE for CCL procedures during the COVID-19 pandemic.

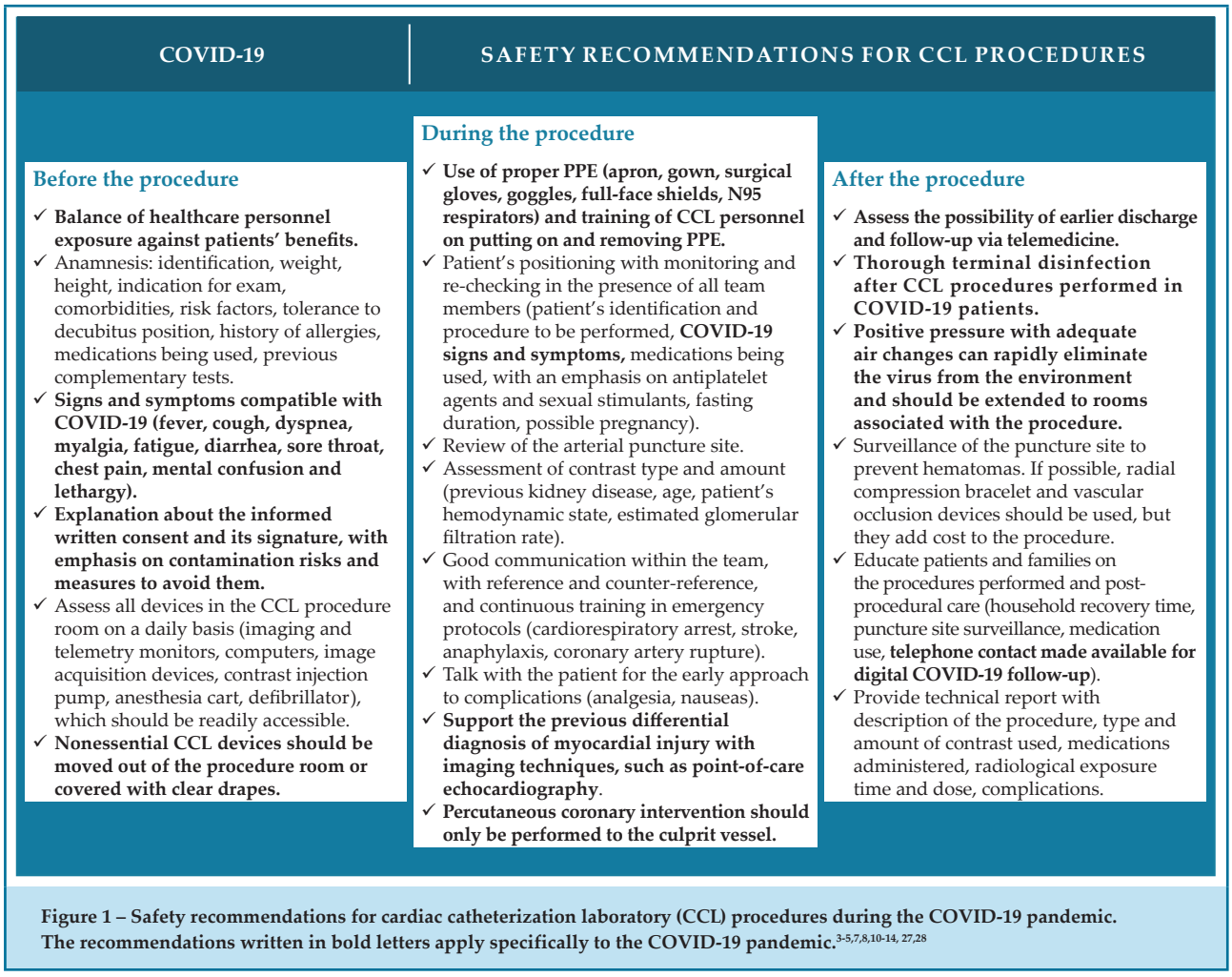

Figure 1 – Safety recommendations for cardiac catheterization laboratory (CCL) procedures during the COVID-19 pandemic. The recommendations written in bold letters apply specifically to the COVID-19 pandemic.[3-5,7,8,10-14, 27,28]

A recent case series of 5700 inpatients with COVI-19 (median age, 63 years; male sex, 60.3%) in the city of New York, United States, has reported a high prevalence of comorbidities, especially cardiovascular ones, as follows: arterial hypertension, 56.6%; coronary artery disease, 11.1%; heart failure, 6.9%; obesity, 41.7%; and diabetes, 33.8%. In-hospital lethality rate was 21%, which increased to 88% among those requiring mechanical ventilation. In addition, the authors have reported that most patients maintained their routine medications, such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. These data reinforce the need to maintain the traditional treatment of patients with heart diseases to avoid decompensation during the pandemic.[29]

The challenges presented during the COVID-19 pandemic are huge, not only the approach of patients with cardiovascular diseases, who need to continue their treatments regardless of having or not COVID-19, but also the management of the complex cardiovascular manifestations of SARS-CoV-2 infection, such as myocarditis, Takotsubo syndrome and myocardial injury, which can mimic ST-segment elevation myocardial infarction. In addition, patients usually delay seeking hospital treatment because of fear of contamination.[30,31]

During the COVID-19 pandemic, the established strategies, such as primary angioplasty, remain the standard treatment. These strategies should be performed at hospitals that are well equipped for a timely response and that have a team of specialized professionals wearing the aforementioned PPEs. The fibrinolysis-based strategy should be reserved for situations in which primary angioplasty cannot be performed.[31]

Although interventional cardiology certainly entails more engaging topics than safety, extraordinary times call for

Figure 2 – General safety items for cardiac catheterization laboratory (CCL) procedures during the COVID-19 pandemic. The recommendations written in bold letters apply to the COVID-19 pandemic.[3-5,7,8,10-13-28]

extraordinary measures. It is essential to revisit the different aspects of protection for patients and healthcare personnel in the CCL, as well as to tailor them to the COVID-19 scenario.

Health systems around the world have been overwhelmed for months. However, unlike ventilators and wards, healthcare personnel cannot be 'manufactured' urgently, mainly highly specialized professionals, such as CCL staff.[32]

All activities performed in CCL rooms need to be restructured, and registries should be kept to quantify the effects of COVID-19 on the treatment of patients with cardiovascular diseases. In doing so, we will be able to learn from this pandemic and thereby both add value to this field and contribute to a rapidly growing body of knowledge on COVID-19.

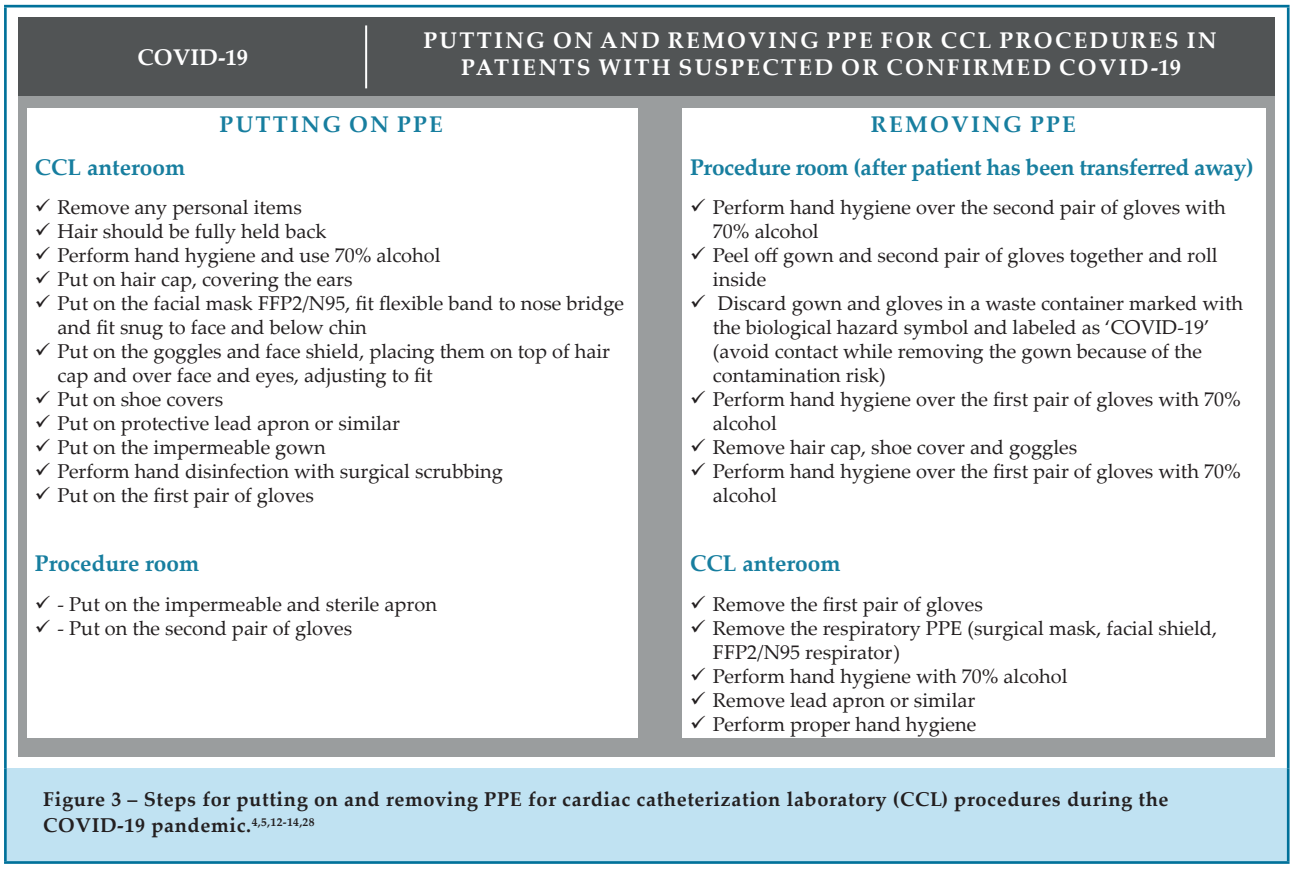

Figure 3 – Steps for putting on and removing PPE for cardiac catheterization laboratory (CCL) procedures during the COVID-19 pandemic.[4,5,12-14,28]

Author contributions

Conception and design of the research: Mariano GZ, Lenke V, Paiva MSM, Oliveira GMM. Acquisition of data: Mariano GZ, Lenke V, Paiva MSM, Oliveira GMM. Analysis and interpretation of the data: Mariano GZ, Lenke V, Paiva MSM, Oliveira GMM. Writing of the manuscript: Mariano GZ, Lenke V, Paiva MSM, Oliveira GMM. Critical revision of the manuscript for intellectual content: Mariano GZ, Lenke V, Paiva MSM, 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 graduation program.

References

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis. 2020;20(5):533-4.
2. Oliveira GMM, Pinto FJ. COVID-19: *A Matter Close to the Heart.* Int J Cardiovasc Sci. 2020; ahead print. Epub Apr 17,2020.
3. Driggin E, Madhavan MV, Bikdeli B, Chuich T, Laracy J, Bondi-Zoccai G, et al. Cardiovascular Considerations for Patients, Health Care Workers, and Health Systems During the Coronavirus Disease 2019 (COVID-19) Pandemic, J Am Coll Cardiol. 2020 Mar 18, Pii:S0735-1097(20)34637-4 [Epub ahead of print]
4. Welt FGP, Shah PB, Aronow HD, Bortnick AE, Henry TD, Sherwood MW, et al., from the American College of Cardiology's (ACC) Interventional Council and the Society of Cardiovascular Angiography and Intervention (SCAI), Catheterization Laboratory Considerations During the Coronavirus (COVID-19) Pandemic: From ACC's Interventional Council and SCAI. J Am Coll Cardiol. 2020; doi: https://doi.org/10.1016/j.jacc.2020.03.031.
5. Sociedade Brasileira de Hemodinâmica e Cardiologia Intervencionista. (SBHCI). Comunicado n° 04/2020. Posicionamento da Sociedade Brasleira de Hemodinâmica e Cardiologia Intervencionista sobre a Pandemia COVID-19. [Citado em 2020 Apr 30] Disponível em: sbhci.org/post/comunicado 04-2020 www.sbhci.org.br
6. Wu Z, McGoogan JM. Characteristics of and Important Lessons from the Coronavirus Disease 2019 (COVID-19) Outbreak in China:Summary of a Report of 72314 Cases From the Chinese Center for Disease Control

and Prevention. JAMA.2020 Feb 24. [Cited 2020 April 16]. Available from:https: Available from: doi: 10.1001/jama/2020.2448

7. Huh S. How to train health personnel to protect themselves from SARS-CoV-2 (novel coronavirus) infection when caring for a patient or suspected case.J educ Eval Health Prof.2020;17:10. Doi:10.3352/jehp.2020.17.18

8. Naidu SS,Aronow H, Box L, Daffy PL, Kolansky DM, Kupfer JM. SCAI Expert Consensus Statement: 2016 Best Practices in the Cardiac Catheterization Laboratory: (Endorsed by the Cardiological Society of India, and Sociedad Latino Americana de Cardiologia Intervencionista; Affirmation of Value by the Canadian Association of Interventional Cardiology–Association Canadienne de Cardiologie d'intervention)*. Cath Cardiovasc Interv. 2016;88(3):407-23.

9. Zeng J, Huang J, Pan L. How to balance acute myocardial infarction and COVID-19: the protocols from Sichuan Provincial People's Hospital. Intensive Care Med. 2020 Feb 26. doi: 10.1007/s00134-020-05993-9

10. Koh D. Occupational risks for COVID-19 infection. Occup Med (London). 2020;70(1):3-5. doi:10.1093/occmed/kqaa036

11. Costa I, Bittar C, Rizk S, Araujo Filho AE, Santos KQ, Machado T, et al. The Heart and COVID-19: What cardiologists need to know. Arq Bras Cardiol-diol. 2020; [online].ahead print, PP.0-0. DOI: https://doi.org/10.36660/abc.20200279

12. Szerlip M, Anwaruddin S, Aronow HD, Cohen MG, Daniels MJ, et al. Considerations for Cardiac Catheterization Laboratory Procedures Dur-ing the COVID-19 Pandemic. Perspectives from the Society for Cardiovascular Angi-ography and Interventions Emerging Leader Mentorship (SCAI ELM) Members and Grad-uates. doi: 10.1002/ccd.28887

13. Tarantini G, Fraccaro C, Chieffo A, Marchese A, Tarantino F, Rigattieri S, et al. Italian Society of Interventional Cardiology (GISE) position paper for Cath lab-specific preparedness recommendations for healthcare providers in case of suspected, probable or confirmed cases of COVID-19. Catheter Cardiovasc Interv. 2020; 1–5. https://doi.org/10.1002/ccd.28888

14. ESC Guidance for the Diagnosis and Management of CV Disease during the COVID-19 Pandemic. Eur Soc Cardiol. 2020 Apr 21. [Cited in 2020 April 21]. Available from: https://www.escardio.org/Education/COVID-19-and-Cardiology/ESC-COVID-19-Guidance

15. Shereen MA, Shereen MA, khan S, Kazmi A, Bashir N, Siddique R. COVID-19 infection: Origin, transmission, and characteristics of human coronaviruses. J Adv Res. 2020;24:91-8. doi.org/10.1016/j.jare.2020.03.005

16. Andreassi MG, Picalluga E, Guagliumi G, Del Greco M, Gaita F, Picano F. Occupational health risks in cardiac catheterization laboratory workers. Circ Cardiovasc Interv. 2016; 9(4):e003273.

17. Christopoulos G, Makke L, Kolsia A, Rangan BV, Roesle M. Optimizing Radiation Safety in the Cardiac Catheterization Laboratory: A Practical Approach. Catheter Cardiovasc Interv. 2016;87(2):291-301.

18. Sun Z, Abazis A, Yusof AK. Radiation-induced noncancer risks in interventional cardiology: optimisation of procedures and staff and patient dose reduction. Biomed Res Int. 2013;2013.976962

19. Fetterly KA, Mathew V, Lennon R, Bell MR, Holmes DR Jr, Rihal CS, et al. Radiation Dose Reduction in the Invasive Cardiovascular Laboratory Implementing a Culture and Philosophy of Radiation Safety. JACC:Cardiovasc Interv. 2012;5(8):866-73.

20. Agarwal S, Parashar A, Ellis SG, Heupler FA Jr, Lau E, Tuzcu EM, et al. Measures to reduce radiation in a modern cardiac catheterization laboratory. Circ Cardiovasc Interv, 2014;7(4):447-55.

21. Agência Nacional de Vigilância Sanitária. (Anvisa). Gerência de Vigilância e Monitoramento em Serviços de Saúde Gerência Geral de Tecnologia em Serviços de Saúde. Nota Técnica GVIMS/GGTES/Anvisa No 04/2020 orientações para serviços de saúde: medidas de prevenção e controle que devem ser adotadas durante a assistência aos casos suspeitos ou confirmados de infecção pelo novo coronavirus (SARS-COV-2); 31 mar. 2020.

22. Best PJ, Skelding KA, Mehran R, Chieffo A, Kunadian V, Madan M,et al. SCAI Consensus Document on Occupational Radiation Exposure to the Pregnant Cardiologist and Technical Personnel. Catheter Cardiovasc Interv. 2011 Feb 1;77(2):232-41.

23. Gurm HS, Dixon SR, Smith DE, Share D, Lafonde T, Greenbaum A, et al. Renal Function-Based Contrast Dosing to Define Safe Limits of Radiographic Contrast Media in Patients Undergoing Percutaneous Coronary Interventions. J Am Coll Cardiol. 2011;58(9):907-14.

24. Kern M. Cath Lab Safety. CathLabDigest. 2020 Apr 24;22(4)

25. Picano E. The appropriate and justified use of medical radiation in cardiovascular imaging: a position document of the ESC Associations of Cardiovascular Imaging, Percutaneous Cardiovascular Interventions and Electrophysiology. Eur Heart J. 2014; 35(10):865-72.

26. Azzalini L, Laricchia A, Regazzoli D, Mitomo S, Hachinohe D, Bellini B,et al. Ultra-Low Contrast Percutaneous Coronary Intervention to Minimize the Risk for Contrast-Induced Acute Kidney Injury in Patients With Severe Chronic Kidney Disease. J Invasive Cardiol. 2019 Jun;31(6):176-82. Epub 2019 Mar 15

27. Romaguera R, Gonzalez IC, Ojeda S, Jimenez-Candil J, Calvo D, Garcia Seara J, et al. Gestión de salas de procedimientos invasivos cardiológicos durante el brote de coronavirus COVID-19. Documento de consenso de la Asociación de Cardiología Intervencionista y la Asociación del Ritmo Cardiaco de la Sociedad Española de Cardiología Rafael Romagueraa. REC Interv Cardiol. REC Interv Cardiol. 2020; ahead print. Epub Mar 16,2020. doi: https://doi.org/10.24875/RECIC.M20000114.

28. Ierardi AM, Wood BJ, Gaudino C, Angileri SA, Jones EC, Hauseggers K, et al. How to Handle a COVID-19 Patient in the Angiographic Suite. Cardiovasc Intervent Radiol. 2020 Apr 10. doi: https://doi.org/10.1007/s00270-020-02476-8

29. Richardson S; Hirsch JS, Mangala N, Crawford JM, McGinn T, Davidson K, and Northwell COVID-19 Research Consortium. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the NewYork City Area. JAMA. 2020 Apr 22 doi:10.1001/jama.2020.6775

30. Rosenbaum L. The Untold Toll — The Pandemic's Effects on Patients without Covid. N Engl J Med. 2020 Apr 17. Doi:10.1056/NEJMms2009984

31. Mahmud E, Dauerman HL, Welt FG, Messenger JC, Rao SV, Grines C, et al. Management of acute myocardial infarction during the COVID-19 pandemic,. J Am Coll Cardiol. 2020 April 20. doi: https://doi.org/10.1016/j.jacc.2020.04.039.

32. McCartney M. Medicine: before COVID-19, and after. The art of medicine-perspectives. Lancet. 2020 Ar 20;395(10232):1248-9.

International Journal of Cardiovascular Sciences. 2020; 33(3):295-298

CASE REPORT

Acute Pericarditis in Crohn's Disease under Pharmacological Immunosuppression: A Diagnostic and Therapeutic Dilemma

Maria Trêpa, Isabel Neves, Marta Salgado, Graziela Carvalheiras, Vasco Dias

Centro Hospitalar do Porto, Porto - Portugal

Introduction

Acute pericarditis in young patients usually has a benign course. However, in those with autoimmune diseases it is mandatory to consider the risk of opportunistic infections, and of association with the underlying disease or immunomodulatory drugs. This case report aims to show possible strategies for diagnosis and treatment of this particularly complex group of patients.

Case Report

A 40-year-old woman, with Crohn's disease diagnosed in 2009 was admitted to the emergency department with a 1-week history of fever, dyspnea and pleuritic chest pain. She was taking adalimumab (anti-TNFα), and azathioprine was started after a negative screening for tuberculosis (TB) done by *interferon gamma release assay* (IGRA). Upon admission, examinations revealed pulmonary and peripheral congestion, and hypoxemia (PaO_2: 60 mmHg). C-reactive protein was elevated (92 mg/L) and there was normocytic anemia (Hb: 7.9 mg/dL) and lymphopenia (670/μL). Electrocardiogram showed T wave flattening and transthoracic echocardiogram (echo) showed moderate pericardial effusion and thickening of layers. Bi-ventricular function was normal.

A diagnosis of acute pericarditis complicated by effusion was assumed. Given the clinical context, she was admitted for further management. She underwent exhaustive examination from which we inferred: (1) no criteria for myopericarditis; (2) no conditions for pericardial drainage (especially effusion on the posterior wall); (3) no microbiological isolates (i.e., bronchial lavage without Koch bacillus isolation); (4) undetermined interferon-γ release assay (IGRA) in two different occasions; (5) negative serology for acute infections (HIV, CMV, EBV, HSV 1 and 2, toxoplasmosis, parvovirus); (6) positive immunological tests foranti-nuclear antibodies (ANA), anti-histones and immunoglobulins G and M; (7) thoracic/abdominal/pelvic computed tomography angiography (Figure 1) with mediastinal and hilar adenopathies (not accessible) with no other findings.

The anti-TNFα was discontinued and she was started on ibuprofen and colchicine, showing an initially good clinical response and decrease of pericardial effusion. However, reassessment 15 days after discharge showed an increase in pericardial effusion and echo criteria for constrictive pericarditis: septal bounce, increased respiratory variability (~40%) of the transtricuspid flow, and dilatation and reduced variability of the inferior vena cava (Figure 2).

Given the unfavorable course, four possible etiologies of pericarditis were considered: (1) idiopathic/viral, (2) bacterial (especially TB), (3) extra-intestinal manifestation of inflammatory bowel disease (IBD) and (4) association with immunomodulation therapy.

The case was presented in a multidisciplinary meeting (including Cardiology, Internal Medicine and Immunology specialists) that concluded that there were no definitive criteria for the cause of pericarditis. However, because of the evidence suggestive of TB (immunosuppression, mediastinal adenopathy and incipient constrictive pericarditis), the real possibility of an adverse outcome if TB was not treated, as well as an increased risk of worsening with the use of corticosteroid

Keywords

Crohn Disease; Pericarditis, Tuberculous; Fever; Tuberculosis; Anti-Bacterial Agents; Antibiotic-Prophylaxis.

Mailing Address: Maria Trêpa
Largo Prof. Abel Salazar, nº 1. Postal Code: 4099-001, Porto – Portugal.
E-mail: maria_trp@hotmail.com

DOI: 10.5935/2359-4802.20190033

Manuscript received Ocotober 28, 2018; revised manuscript October 28, 2018; accepted November 22, 2018.

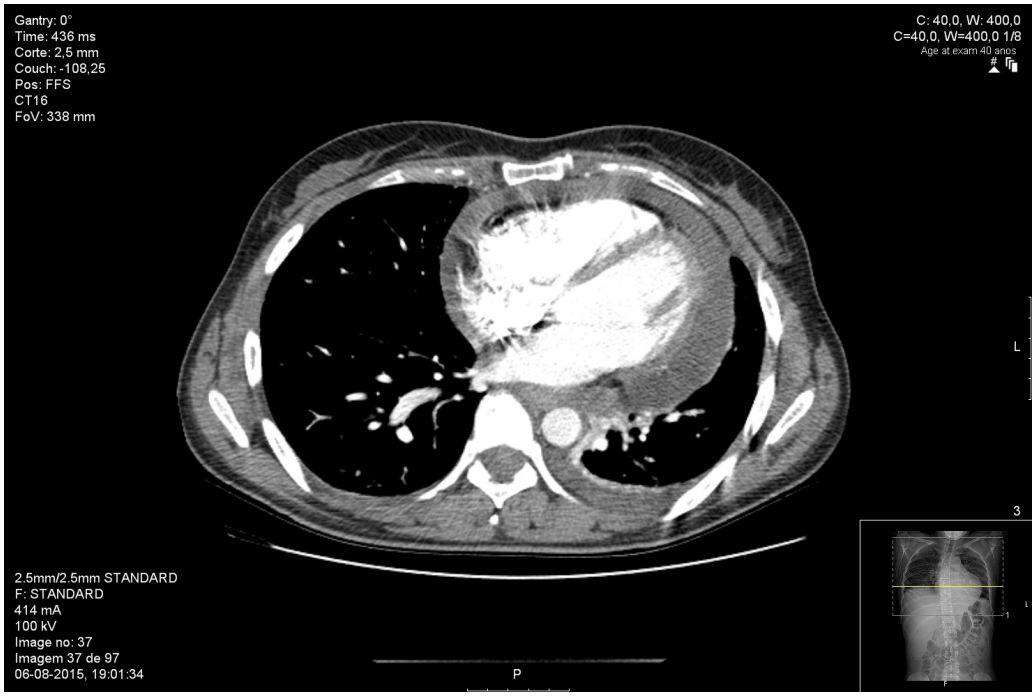

Figure 1 - Thoracic computed tomography angiography showing moderate pericardial effusion with asymmetric distribution.

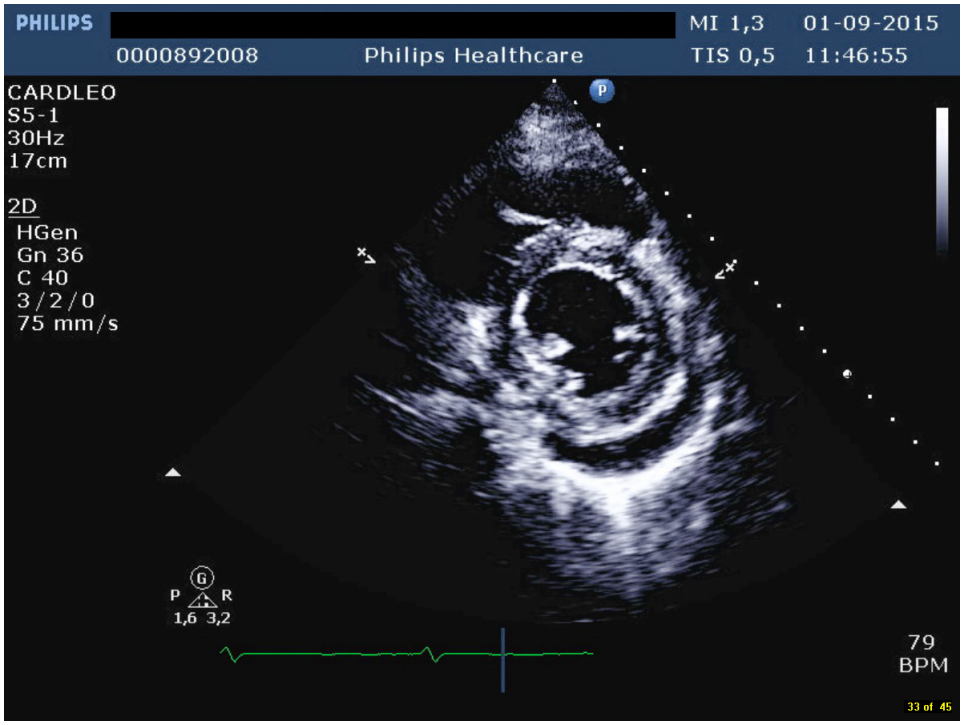

Figure 2 - Control echocardiogram performed two weeks after treatment initiation showing thickening of pericardial layers and moderate effusion, septal bounce and increased respiratory variability of the transtricuspid flow.

alone, we decided to assume the presumptive diagnostis of tuberculous pericarditis. We maintained the Anti-TNFα discontinued and started corticosteroids and anti-TB drugs (isoniazid and rifampicin for 6 months and pyrazinamide and ethambutol for 2 months).

The patient showed progressive improvement. Control echocardiography at one and eight months after ending TB-treatment revealed complete resolution of effusion and of constriction criteria.

Discussion

As the number of immunosuppressed patients grows, the diagnostic and therapeutic dilemma reported here will probably increase since these patients are particularly complex to manage. Viral etiology of pericarditis remains the most frequent one, but it is mandatory to consider not only the association with the underlying autoimmune disease or with immunomodulation therapy but also the risk of opportunistic infections.

Pericarditis was first described as an extra-intestinal manifestation of irritable bowel disease (IBD) in 1967.[1] It's the most frequently reported cardiac complication and has various presentations, since self-limited forms until severe perimyocarditis and cardiac tamponade,[2-6] The most accepted pathophysiological mechanism is based on the pericardial aggression due to systemic inflammation. An Italian study[3] reported a possible relationship between pericardial effusion and IBD flares. The development of pericarditis does not seem to be related to disease chronicity and has been described both independently and in association with IBD flares.[5]

There are also reports of pericarditis as a complication of immunomodulatory therapy itself, such as associated with 5-ASA, azathioprine and anti-TNFα drugs. Accepted explanations include lupus-like reactions, type 3 hypersensitivity and pro-inflammatory effect of some drugs in serous membranes.[6-8] Usually, there is a clear temporal relation with the initiation of drug use, with improvement after its discontinuation and an increase in anti-histone antibodies. In our case, only the antibody was elevated making it hard to establish a causal relationship. The approach would be to discontinue the offending drug and initiate corticosteroid therapy.

The presumptive diagnosis of TB was assumed after a multidisciplinary meeting and careful consideration. TB prevalence is still high in the urban region where our patient lives. There is a known correlation between anti-TNFα and TB reactivation that justifies mandatory screening before starting treatment. In case of TB pericarditis, a definitive diagnosis is notoriously difficult due to the low yield of cultures and biopsies, and usually a presumptive or exclusion diagnosis is made. The progression to constrictive pericarditis is a potentially serious complication. Without a targeted therapy, up to 50% of patients with effusive-constrictive physiology might progress to constriction in six months.[9] Several studies reinforce the need to consider TB pericarditis in patients at increased risk for TB development with non-benign evolution. In the absence of Koch bacillus isolation from the pericardial fluid or tissue, TB pericarditis is considered likely if the bacillus is isolated from sources and/or if there is a favorable response (based on symptoms and echo) to anti TB-drugs.[10] In patients taking anti-TNFα drugs, there is a particularly increased risk of TB, frequently extra-pulmonary.

The impossibility of performing pericardiocentesis was a limiting factor in our diagnostic approach. However, in the absence of other strong diagnostic hypotheses, and given the treatment with anti-TNFα, the high TB prevalence, the angioCT and echo findings, and the possibility of irreversible adverse outcome if untreated, we assumed the presumptive diagnosis of TB pericarditis. The good response to treatment favored our decision.

This case report portraits the difficulties in the diagnosis of these patients, but also provides possible therapeutic strategies. In the absence of strong recommendations for such complex cases, we trust in experience and multidisciplinary discussion. These cases should be managed with specific strategies defined individually.

Author contributions

Conception and design of the research: Trêpa M, Neves I, Dias V. Acquisition of data: Trêpa M, Neves I, Dias V. Analysis and interpretation of the data: Trêpa M, Salgado M, Carvalheiras G. Writing of the manuscript: Trêpa M. Critical revision of the manuscript for intellectual content: Trêpa M, Neves I, Salgado M, Carvalheiras G, Dias V.

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. Young PC. Colonic and systemic manifestations of chronic ulcerative colitis. Med Clin North Am. 1967;51(4):1011-3.
2. Bernstein CN, Blanchard JF. The clustering of other chronic inflammatory diseases in inflammatory bowel disease: a population-based study. Gastroenterology.2005;129(3):827-36.
3. Bragagni G, Brogna R, Franceschetti P, Zoli G.et al. Cardiac involvement in Crohn's disease: echocardiographic study. J Gastroenterol Hepatol. 2007. 22(1):18-22.
4. Patwardhan RV, Heilpern RJ, Brewster AC, Darrah JJ. Pleuropericarditis: an extraintestinal complication of inflammatory bowel disease. Report of three cases and review of literature. Arch Intern Med. 1983;143(1):94-6.
5. Stasinopoulou P, Kaziani A, mantzaris G, Roussos A, Skoutelis A. Parallel manifestation of Crohn's disease and acute pericarditis: a report of two cases. Int J Colorectal Dis. 2007;22(9):1123-5.
6. Kiyomatsu H, Kawai K, Tanaka T, Tanaka J, Kiyomatsu T, Nozawa H, et al. Mesalazine-induced pleuropericarditis in a patient with Crohn's disease. Intern Med. 2015;54(13):1605-8.
7. Burke JP, Kelleher B, Ramadan S, Quinlan M, Sugrue D, O'Donovan MA, et al. Pericarditis as a complication of infliximab therapy in Crohn's disease. Inflamm Bowel Dis. 2008;14(3):428-9.
8. Devasahayam J, Pillai U. A rare case of pericarditis, complication of infliximab treatment for Crohn's disease. J Crohns Colitis. 2012;6(6):730-1.
9. Adler Y, Charron F, Imazio M, Badano L, Barón-Esquivias G, Bogaert J. 2015 ESC Guidelines for the Diagnosis and Management of Pericardial Diseases. Rev Esp Cardiol. (Engl Ed). 2015;68(12):1126.
10. Stout J, von Reyn FC, Baron EL. Tuberculous pericarditis. [internet]. [Cited in 2017 May 12]. Available from: https://www.uptodate.com/contents/tuberclous-pericarditis

International Journal of Cardiovascular Sciences. 2020; 33(3):299-302

CASE REPORT

Complete Atrioventricular Block and Cardiopulmonary Involvement in Rapidly Progressive Systemic Sclerosis

Eduarda Cal Viegas, Diane Xavier de Ávila, Eduardo Nani Silva, Luís Otávio Cardoso Mocarzel, Ronaldo Altenburg Gismondi

Universidade Fluminense Federal (UFF), Rio de Janeiro, RJ - Brazil

Abstract

The heart and lung are target organs in systemic sclerosis (SSc) and similar symptoms (dyspnea and cough) may make the differential diagnosis between the two lesions difficult. In addition, complete atrioventricular block (CAVB) is a rare complication of this disease. This case report is about a patient with SSc and pulmonary fibrosis who was admitted to the emergency room with CAVB, heart failure (HF) and progressive worsening of the underlying disease.

Introduction

Systemic sclerosis (SSc) is a multifactorial autoimmune connective tissue disease, with high morbidity and mortality rates, whose prevalence in the general population is 5%.[1,2] It is characterized by vascular injury and fibrosis of the skin and internal organs, the heart and lungs being the most frequently involved organs.[3,4] It is divided into 2 main subsets based on the extent of cutaneous involvement, limited and diffuse; the latter is associated with more visceral involvement.[1-3] Cardiac involvement can affect the pericardium, the myocardium, and the conduction system.[4-7] Complete atrioventricular block (CAVB) is the least common conduction abnormality.[4-7] Here, we report a case of rapidly progressive systemic sclerosis complicated by CAVB and heart failure (HF).

Keywords

Heart Failure; Atrioventricular Block; Scleroderma, Systemic; Hypertension, Pulmonary; Pulmonary Fibrosis.

Case Report

We report the case of a 50-year-old black man diagnosed with rapidly progressive diffuse Systemic Sclerosis, confirmed by clinical and serological tests[8] under treatment with methotrexate, folic acid and monthly pulse therapy with methylprednisolone and cyclophosphamide. He sought care in the emergency room presenting with a clinical picture of HF, with progressive worsening in the last three months, in addition to evening fever. On physical examination he presented tachypnea, with no signs of respiratory effort, cold extremities, slow capillary filling, JVP at 45 degrees and cannon "a" wave in JVP and diffuse skin thickness. Blood pressure 110/70 mmHg, heart rate 42 bpm and respiratory rate 26 bpm. The examination of the thorax revealed left deviation of the ictus cordis, regular heart rate, presence of LV third heart sound, a grade 2/6 systolic murmur and a grade 3/6 tricuspid regurgitation murmur. Lungs with bilateral crackles. Hepatomegaly with pain on palpation. Bilateral lower extremity edema (2+/4+). Electrocardiogram (ECG) showed CAVB (Figure 1).

Therapy with intravenous furosemide, spironolactone and enalapril was initiated upon admission, and the patient was referred to the cardiac intensive care unit. On the second day of hospitalization, a permanent dual-chamber, epicardial pacemaker was implanted (Figure 2).

The transthoracic echocardiography (TTE) revealed increased left cavities, diffuse hypokinesia, LVEF of 38% (Simpson's rule), moderate mitral and tricuspid regurgitation and PSAP 65 mmHg. Thoracic computed tomography (CT) displayed ground-glass opacity distributed diffusely through both lungs, bronchiectasis, inter and intralobular septal thickening and paraseptal emphysema in the upper lobes. Laboratory tests showed

Mailing Address: Eduarda Cal Viegas
Rua Marques de Paraná, 303. Postal Code: 24033-900, Centro, Niterói, RJ – Brazil.
E-mail: eduardacviegas@hotmail.com

DOI: 10.5935/2359-4802.20190069

Manuscript received on March 06, 2018, revised manuscript on May 30, 2018, accepted on November 01, 2018.

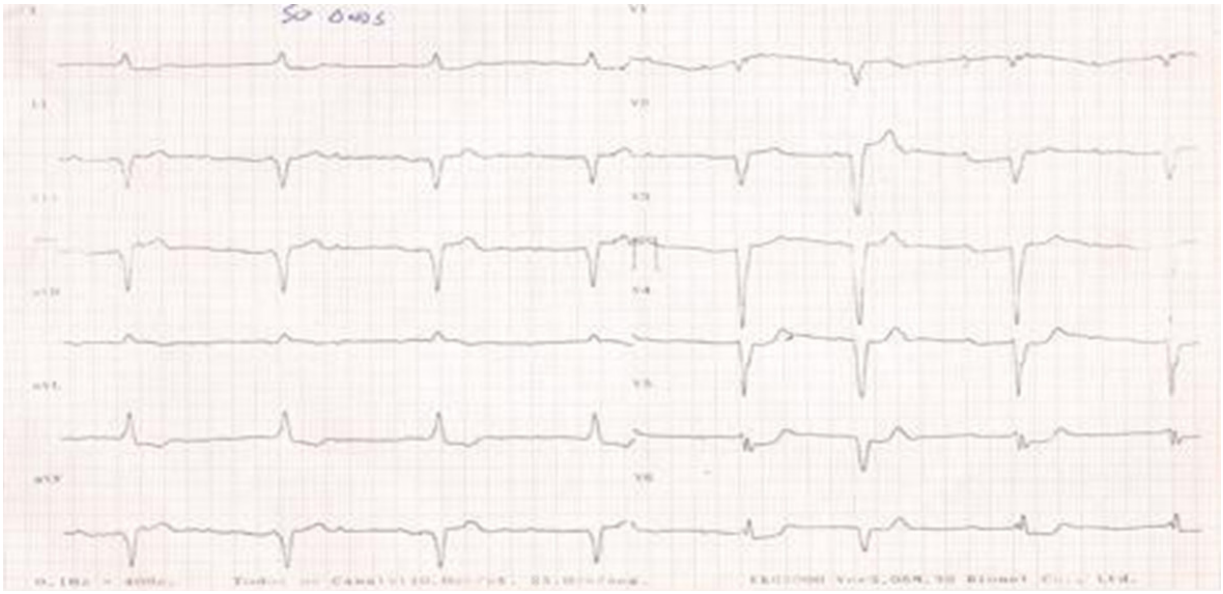

Figure 1 - 12-lead ECG showing CAVB.

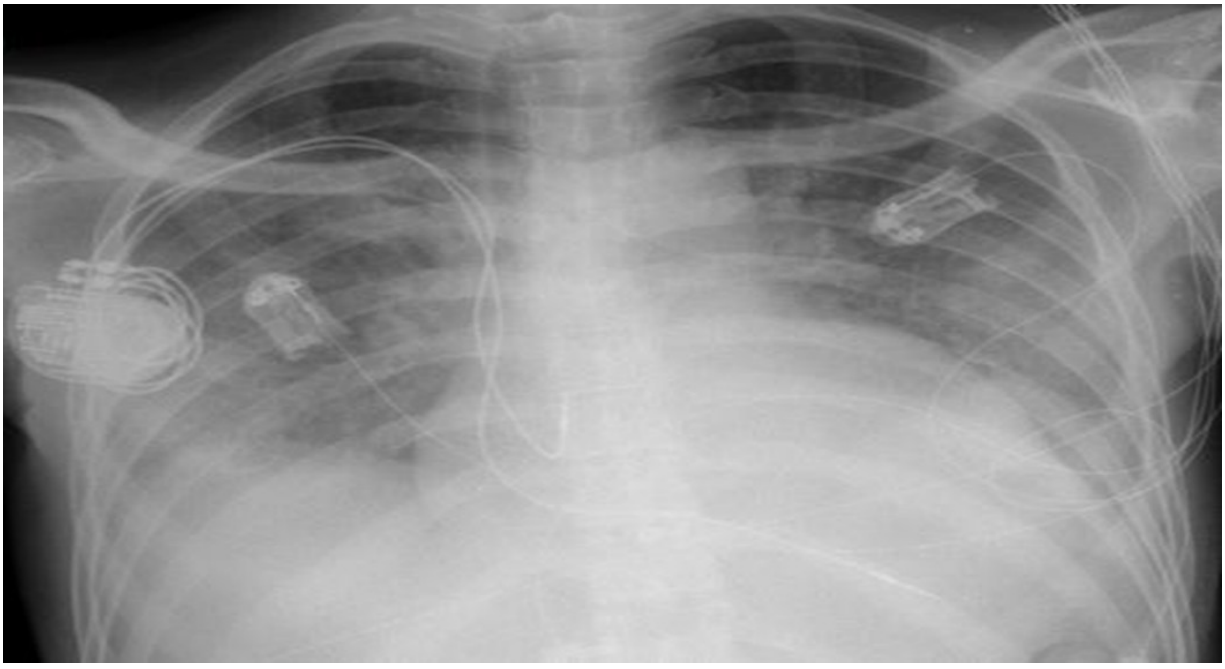

Figure 2 - Bedside PA chest x-ray showing cardiomegaly and pulmonary congestion. In addition, a right-sided dual-chamber pacemaker can be observed.

the presence of anemia, increased CRP and increased NT-proBNP levels (Table 1).

Despite correction of the conduction disorder, there was clinical worsening of HF and of the underlying disease activity with the ongoing treatment, thus a decision was made to start rituximab as rescue therapy[8] of SSc. There was progressive worsening of HF symptoms despite optimal medical therapy and the patient evolved to death due to refractory cardiac shock.

Discussion

Cardiac involvement in SSc includes pericarditis, myocardial disease and conduction abnormalities. Between 25% and 75% of the patients have electrocardiographic abnormalities, such as ST segment changes, ventricular or supraventricular arrhythmias and conduction disorders.[2] The most frequent conduction abnormality in SSc patients are left branch block, first-degree AV block, left anterior fascicular block and right branch block. CAVB is a rare complication that affects less than 2 percent of patients.[4-7,9] In a large international series of 3656 SSc patients, conduction disorders were observed in 12.7% of them.[10]

Lung disease is seen in 61% of SSc patients,[11] and the most prevalent clinical manifestations are pulmonary fibrosis and pulmonary vascular disease, which cause arterial pulmonary hypertension (APH).[1-4,8] The prevalence of APH varies according with the diagnostic method used: between 8 and 12%, by right cardiac catheterization, and about 38% by TTE.[1,2,4] APH is often diagnosed late in the evolution of the disease, as observed in our patient.

Patients who have clinically evident cardiopulmonary involvement evolve with a worse prognosis;[1-4,8] therefore screening of subclinical involvement in patients with SSc should be considered. Nevertheless, data on the best screening method are not well-defined yet. Initial investigation of cardiac involvement must include ECG, TTE and cardiac biomarker testing, such as brain natriuretic peptide (BNP) or its inactive form NT-proBNP.[2] In asymptomatic patients, without confirmed diagnosis by initial examination, the 24h Holter and cardiac imaging exams, such as magnetic resonance imaging, may be indicated.[8,11]

The rapid progression of the underlying disease, refractoriness to HF treatment and the significant presence of APH contributed to the patient's death.

Table 1 - Patient laboratory data

	Admission	D14
Hemoglobin (g/dL)	10.8	9.8
Hematocrit (%)	34.2	30.9
Leukocytes (mm^3)	10,700	10,600
Bands (%)	1	2
CRP (mg/dL)	8.91	13.61
INR	1.15	
Urea (mg/dL)	73	65
Creatinine (mg/dL)	1.06	0.86
Sodium (mEq/L)	133	130
Potassium (mEq/dL)	4.2	4.4
Nt-proBNP (pg/mL)	40,643	101,821

Conclusion

The reported case reinforces the importance of early diagnosis of cardiac and pulmonary involvement in SSc, aiming at better therapeutic approaches and the reduction of morbidity and mortality.

Author contributions

Conception and design of the research: Nani ES, Mocarzel LOC, Gismondi RA. Acquisition of data: Viegas EC, Ávila DX. Writing of the manuscript: Viegas EC, Ávila DX. Critical revision of the manuscript for intellectual content: Nani ES, Mocarzel LOC, Gismondi RA.

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 graduation work submitted by Eduarda Cal Viegas, from *Universidade Federal Fluminense*.

Ethics approval and consent to participate

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

References

1. Desbois AC, Cacoub P. Systemic sclerosis: an update in 2016. Autoimmun Rev. 2016;15(5):417-26.
2. Vandecasteele EH, De Pauw M, Brusselle G, Decuman S, Piette Y, De Keyser F, et al. The heart and pulmonary arterial hypertension in systemic sclerosis. Acta Clin Belg. 2016;71(1):1-18.
3. Denton CP, Khanna D. Systemic sclerosis. Lancet. 2017;390(10103):1685-99.
4. Ciurzyński M, Bienias P, Szewczyk A, Lichodziejewska B, Błaszczyk M, Liszewska-Pfejfer D, et al. Advanced systemic sclerosis complicated by pulmonary hypertension and complete atrioventricular block: a case report. Med Sci Monit. 2007;13(10):CS124-7.
5. Femenia F, Arce M, Arrieta M. Systemic sclerosis complicated with syncope and complete AV block. Medicina (B Aires). 2010;70(5):442-4.
6. Windesheim JH, Parkin TW. Electrocardiograms of ninety patients with acrosclerosis and progressive diffuse sclerosis (scleroderma). Circulation. 1958;17(5):874-81.
7. Vacca A, Meune C, Gordon J, Chung L, Proudman S, Assassi S, et al. Cardiac arrhythmias and conduction defects in systemic sclerosis. Rheumatology (Oxford). 2014;53(7):1172-7.
8. Elhai M, Avouac J, Kahan A, Allanore Y. Systemic sclerosis : recent insights. Joint Bone Spine. 2015;82(3):148-53.
9. Moyssakis I, Papadopoulos DP, Tzioufas AG, Votteas V. Complete heart block in a patient with systemic sclerosis. Clin Rheumatol. 2006;25(4):551-2.
10. Walker UA, Tyndall A, Czirják L, Denton C, Farge-Bancel D, Kowal-Bielecka O, et al. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials And Research group database. Ann Rheum Dis. 2007;66(6):754-63.
11. Hachulla E, de Groote P, Gressin V, Sibilia J, Diot E, Carpentier P, et al. The three-year incidence of pulmonary arterial hypertension associated with systemic sclerosis in a multicenter nationwide longitudinal study in France. Arthritis Rheum. 2009;60(6):1831-9.

NEWS

Calendar

XLVII Congresso Paranaense de Cardiologia & International Cardiology Meeting
Centro de Eventos Expo Unimed
August 14-15, 2020

XXXII Congresso da SBC/ES
Aroso Paço Hotel
August 20-22, 2020

37º Congresso de Cardiologia da SOCERJ
Centro de Convenções SulAmérica
September 16-18, 2020

XVII Congresso Brasileiro de Cardiogeriatria - DECAGE 2020
Hotel Plaza São Rafael - POA
October 30-31, 2020

Congresso SBHCI 2020
Expominas - BH/MG
November 04-06, 2020

XVII Congresso DHA
Hotel Clarion Goiânia Orion
November 05-07, 2020

SOBRAC 2020
Hotel Sharaton Santos - SP
November 05-07, 2020

75º Congresso Brasileiro de Cardiologia
November 20-23, 2020
Centro Internacional de Convenções do Brasil (CICB) – Brasília

XXVI Congresso Nacional do DERC
Centro Fecomércio de Eventos - SP
November 26-28, 2020

26º Congresso Brasileiro de Cardiologia e Cirurgia Cardiovascular Pediátrica
Royal Tulip Brasília Alvorada
November 26-28, 2020

47º Congresso da Sociedade Brasileira de Cirurgia Cardiovascular
PUCRS - POA
March 26-27, 2021

41º Congresso da Sociedade de Cardiologia do Estado de São Paulo
Transamerica Expo Center
June 03-05, 2021

DEIC 2020/2021
Hotel Royal Palm Plaza - Campinas
June 24-26, 2021

30º Congresso do Sociedade Mineira de Cardiologia
Ouro Minas Palace Hotel
July 01-03, 2021

SEE IN THE NEXT EDITION

Vol. 33, Nº 4, July e August 2020

INTERNATIONAL JOURNAL OF
Cardiovascular
SCIENCES

Call for Papers

Chagas Heart Disease

The International Journal of Cardiovascular Sciences (IJCS) is now accepting papers for a special theme issue on Chagas Heart Disease, to be published in September 2020. The Editors are looking for articles focusing the diagnosis, treatment, epidemiological aspects, and pathogenesis of the disease, as well as immune mechanisms involved in myocardial injury. The deadline for submission is May 30. Interested authors should submit their papers online at ScholarOne System. For questions or general inquiries, email revistaijcs@cardiol.br.

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

Authors can submit their manuscripts through the Manuscript Tracking System. To submit your paper visit: https://mc04.manuscriptcentral.com/ijcs-scielo.

SCHOLARONE™

Submission Deadline	June 30th, 2020
Publication Date	November/December 2020

SOCIEDADE BRASILEIRA DE CARDIOLOGIA
SBC
1943

INTERNATIONAL JOURNAL OF

Cardiovascular SCIENCES