INTERNATIONAL JOURNAL OF

Cardiovascular SCIENCES

EDITORIAL

Cardiology Journals from Portuguese-Speaking Countries: Challenges and Opportunities

ORIGINAL ARTICLES

24-Hour Ambulatory Blood Pressure Monitoring Predicts Outcomes of Hypertensive Patients in Primary Care: A Cohort Study

Are Patients' Blood Pressure Levels Being Routinely Measured in Medical Offices?

12-Month Clinical Follow-Up of Patients Undergoing Early Invasive Strategy by the Transradial or Transfemoral Approach with Vascular Closure Device

Probabilistic Model for Prediction of Prognostics in Myocardial Revascularization: Complications in Coronary Surgery

Are Body Fat and Uric Acid associated with Cardiovascular Risk Scores? Cross-Sectional Analysis in the PROCARDIO-UFV Trial

Green Tea Attenuates Hypotension Induced by Physical Exercise: A Randomized, Placebo Controlled Study

Study of Dabigatran Use in a Brazilian Public Hospital Specialized in Cardiology

REVIEW ARTICLE

Predictors of Metabolic Syndrome in the Elderly: A Review

VIEWPOINT

Detailing Peripheral Arterial Tonometry in Heart Failure. An Endothelial Function Evaluation

CASE REPORTS

Cardiac Memory, an Underdiagnosed Condition

A Transcatheter Aortic Valve Implantation Without Aortography Guidance Due To Vascular Access Constraints Or Limitations

Volume 30 - Number 4 | July / August | ISSN print 2359-4802 | ISSN online 2359-5647

INTERNATIONAL JOURNAL OF
Cardiovascular Sciences

SUMMARY

- **Editorial**

Cardiology Journals from Portuguese-Speaking Countries: Challenges and Opportunities 283
Luiz Felipe P. Moreira

- **Original Articles**

24-Hour Ambulatory Blood Pressure Monitoring Predicts Outcomes of Hypertensive Patients in Primary Care: A Cohort Study 285
Guilherme Brasil Grezzana, Airton Tetelbon Stein, Lucia Campos Pellanda

Are Patients' Blood Pressure Levels Being Routinely Measured in Medical Offices? 293
Israel Guilharde Maynarde, Thiago Veiga Jardim, Weimar Kunz Sebba Barroso de Souza, Ana Luiza Lima Sousa, Andrey Rocha Rocca, Bruna Yana de Carvalho Lin, Natália Mirelle Carrijo dos Santos, Diogo Pereira Santos Sampaio, Xênia Larissa Motta Serafim, Paulo Cesar Brandao Veiga Jardim

12-Month Clinical Follow-Up of Patients Undergoing Early Invasive Strategy by the Transradial or Transfemoral Approach with Vascular Closure Device 299
Pedro Beraldo de Andrade, Luiz Alberto Piva e Mattos, Fabio Salerno Rinaldi, Igor Ribeiro de Castro Bienert, Robson Alves Barbosa, Sérgio Kreimer, Vinícius Cardoso Esteves, Marden André Tebet, André Labrunie, Amanda Guerra de Moraes Rego Sousa

Probabilistic Model for Prediction of Prognostics in Myocardial Revascularization: Complications in Coronary Surgery 307
Valcellos José da Cruz Viana, Felipe Coelho Argolo, Nilzo Augusto Mendes Ribeiro, Augusto Ferreira da Silva Junior, Luis Claudio Lemos Correia

Are Body Fat and Uric Acid associated with Cardiovascular Risk Scores? Cross-Sectional Analysis in the PROCARDIO-UFV Trial 313
Juliane Soares Rodrigues, Alinne Paula de Almeida, Carla de Oliveira Barbosa Rosa, Helen Hermana Miranda Hermsdorff

Green Tea Attenuates Hypotension Induced by Physical Exercise: A Randomized, Placebo Controlled Study 325
Manoel Miranda Neto, Raquel Suelen Brito da Silva, Taís Feitosa da Silva, Fabiano Ferreira de Lima, Alexandre Sérgio Silva

Study of Dabigatran Use in a Brazilian Public Hospital Specialized in Cardiology 334
Luise Barros Martins, Ivis Levy Fernandes Martins, Raíssa Miranda Silva, Flávia Valéria dos Santos Almeida, Christianne Bretas Vieira Scaramello

- **Review Article**

Predictors of Metabolic Syndrome in the Elderly: A Review 343
Carolina Cunha de Oliveira, Emanuelle Dias da Costa, Anna Karla Carneiro Roriz, Lilian Barbosa Ramos, Mansueto Gomes Neto

- **Viewpoint**

Detailing Peripheral Arterial Tonometry in Heart Failure. An Endothelial Function Evaluation 354
Aline Cristina Tavares, Edimar Alcides Bocchi, Guilherme Veiga Guimarães

- **Case Reports**

Cardiac Memory, an Underdiagnosed Condition **359**
Margarida Oliveira, Olga Azevedo, Lucy Calvo, Bebiana Faria, Sílvia Ribeiro, António Lourenço

A Transcatheter Aortic Valve Implantation Without Aortography Guidance Due To Vascular Access Constraints Or Limitations **363**
Oktay Ergene, Hamza Duygu, Volkan Emren, Ugur Kocabas, Levent Cerit

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

Editor

Cláudio Tinoco Mesquita – Hospital Universitário Antônio Pedro (HUAP), Universidade Federal Fluminense (UFF), Niterói, Rio de Janeiro, RJ – Brazil

Associated Editors

Clério Francisco Azevedo Filho (Cardiovascular Imaging Area) – Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, RJ - Brazil

Gláucia Maria Moraes de Oliveira (Clinical Cardiology Area) – Departamento de Clínica Médica, Faculdade de Medicina (FM), Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ - Brazil

Guilherme Vianna e Silva (Interventionist Cardiology Area) – Texas Heart Institute, USA

João Augusto Costa Lima (Integrative Imaging Area) – Johns Hopkins Hospital – Baltimore, USA

Lauro Casqueiro Vianna (Multiprofessional Area) – Faculdade de Educação Física, Universidade de Brasília (UnB), Brasília, DF – Brazil

Miguel Mendes (Ergometric and Cardiac Rehabilitation Area) – Sociedade Portuguesa de Cardiologia, Portugal

Ricardo Mourilhe-Rocha (Heart Failure and Myocardiopathy Area) – Hospital Universitário Pedro Ernesto, Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, RJ - Brazil

EDITORIAL BOARD

Brazil

Andréia Biolo – Faculdade de Medicina, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS – Brazil

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

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

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

Armando da Rocha Nogueira – Departamento de Clínica Médica, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ - Brazil

Carísi Anne Polanczyk – Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS – Brazil

Carlos Eduardo Rochitte – Departamento de Cardiopneumologia, Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP), São Paulo, SP – Brazil

Carlos Vicente Serrano Júnior – Faculdade de Medicina da Universidade de São Paulo, Instituto do Coração (InCor), São Paulo, SP – Brazil

Cláudio Gil Soares de Araújo – Instituto do Coração Edson Saad, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ - Brazil

Cláudio Pereira da Cunha – Departamento de Clínica Médica, Universidade Federal do Paraná (UFPR), Paraná, PR – Brazil

Cláudio Tinoco Mesquita – Hospital Universitário Antônio Pedro (HUAP), Universidade Federal Fluminense (UFF), Niterói, Rio de Janeiro, RJ – Brazil

Denílson Campos de Albuquerque – Faculdade de Ciências Médicas, Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, RJ – Brazil

Denizar Vianna Araujo – Departamento de Clínica Médica, Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, RJ – Brazil

Esmeralci Ferreira – Hospital Universitário Pedro Ernesto (HUPE), Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, RJ - Brazil

Evandro Tinoco Mesquita – Hospital Universitário Antônio Pedro (HUAP), Universidade Federal Fluminense (UFF), Niterói, Rio de Janeiro, RJ – Brazil

Fernando Nobre – Faculdade de Medicina de Ribeirão Preto (FMRP), Universidade de São Paulo, São Paulo, SP – Brazil

Gabriel Blacher Grossman – Serviço de Medicina Nuclear, Hospital Moinhos de Vento, Porto Alegre, RS – Brazil

Henrique César de Almeida Maia – Governo do Distrito Federal (GDF), Brasília, DF - Brazil

Humberto Villacorta Júnior – Hospital Universitário Antônio Pedro (HUAP), Universidade Federal Fluminense (UFF), Niterói, Rio de Janeiro, RJ – Brazil

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

João Vicente Vitola – Quanta Diagnóstico e Terapia (QDT), Curitiba, PR – Brazil

José Geraldo de Castro Amino – Sessão Clínica, Instituto Nacional de Cardiologia (INC), Rio de Janeiro, RJ – Brazil

José Márcio Ribeiro – Clínica Médica (Ambulatório), União Educacional Vale do Aço (UNIVAÇO), Ipatinga, MG - Brazil

Leonardo Silva Roever Borges – Departamento de Pesquisa Clínica, Universidade Federal de Uberlândia (UFU), MG – Brazil

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

Luís Alberto Oliveira Dallan – Serviço Coronariopatias, Instituto do Coração (INCOR), São Paulo, SP - Brazil

Marcelo Iorio Garcia – Clínica de Insuficiência Cardíaca, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ – Brazil

Marcelo Westerlund Montera – Centro de Insuficiência Cardíaca, Hospital Pró Cardíaco (PROCARDIACO), Rio de Janeiro, RJ – Brazil

Marcio Luiz Alves Fagundes – Divisão de Arritmia e Eletrofisiologia, Instituto Nacional de Cardiologia Laranjeiras (INCL), Rio de Janeiro, RJ – Brazil

Marco Antonio Mota Gomes - Fundação Universitária de Ciências da Saúde Governador Lamenha Filho (UNCISAL), Maceió, AL - Brazil

Marco Antonio Rodrigues Torres – Departamento de Medicina Interna, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS – Brazil

Marcus Vinicius Bolivar Malachias – Instituto de Pesquisas e Pós-graduação (IPG), Faculdade de Ciências Médicas de Minas Gerais (FCMMG), Belo Horizonte, MG – Brazil

Maria Eliane Campos Magalhães – Departamento de Especialidades Médicas, Universidade do Estado do Rio de Janeiro (UERJ), Rio de Janeiro, RJ – Brazil

Mário de Seixas Rocha – Unidade Coronariana, Hospital Português, Salvador, BA – Brazil

Maurício Ibrahim Scanavacca – Unidade Clínica de Arritmia, Instituto do Coração do Hospital das Clínicas da FMUSP, São Paulo, SP – Brazil

Nadine Oliveira Clausell – Faculdade de Medicina, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS – Brazil

Nazareth de Novaes Rocha – Centro de Ciências Médicas, Universidade Federal Fluminense, UFF - Rio de Janeiro, RJ – Brazil

Nelson Albuquerque de Souza e Silva – Departamento de Clínica Médica, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ – Brazil

Paola Emanuela Poggio Smanio – Seção Médica de Medicina Nuclear, Instituto Dante Pazzanese de Cardiologia (IDPC) São Paulo, SP - Brazil

Paulo Cesar Brandão Veiga Jardim – Liga de Hipertensão Arterial, Universidade Federal de Goiás (UFGO), Goiânia, GO – Brazil

Ronaldo de Souza Leão Lima – Pós-Graduação em Cardiologia, Universidade Federal do Rio de Janeiro (UFRJ), Rio de Janeiro, RJ – Brazil

Salvador Manoel Serra – Setor de Pesquisa Clínica, Instituto Estadual de Cardiologia Aloysio de Castro (IECAC), Rio de Janeiro, RJ – Brazil

Sandra Cristina Pereira Costa Fuchs – Departamento de Medicina Social, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS – Brazil

Tiago Augusto Magalhães – Ressonância Magnética e Tomografia Cardíaca, Hospital do Coração (HCor), São Paulo, SP – Brazil

Walter José Gomes – Departamento de Cirurgia, Universidade Federal de São Paulo (UFESP), São Paulo, SP – Brazil

Washington Andrade Maciel – Serviço de Arritmias Cardíacas, Instituto Estadual de Cardiologia Aloysio de Castro (IECAC), Rio de Janeiro, RJ – Brazil

Wolney de Andrade Martins – Centro de Ciências Médicas, Universidade Federal Fluminense (UFF), Niterói, Rio de Janeiro, RJ – Brazil

Exterior

Amalia Peix – Instituto de Cardiología y Cirugía Cardiovascular, Havana – Cuba
Amelia Jiménez-Heffernan – Hospital Juan Ramón Jiménez, Huelva – Spain
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
Massimo Francesco Piepoli – Ospedale "Guglielmo da Saliceto", Piacenza – Italy
Raffaele Giubbini – Università degli Studi di Brescia, Brescia – Italy
Ravi Kashyap – International Atomic Energy Agency, Vienna – Austria
Shekhar H. Deo – University of Missouri, Columbia - USA

BIENNIUM BOARD 2016/2017

SOCIEDADE BRAZILEIRA DE CARDIOLOGIA/ BRAZILIAN SOCIETY OF CARDIOLOGY

President
Marcus Vinícius Bolívar Malachias

Vice-President
Eduardo Nagib Gaui

President-Elect
Oscar Pereira Dutra

Scientific Director
Raul Dias dos Santos Filho

Financial Director
Gláucia Maria Moraes Oliveira

Administrative Director
Denilson Campos de Albuquerque

Government Liaison Director
Renault Mattos Ribeiro Júnior

Information Technology Director
Osni Moreira Filho

Communication Director
Celso Amodeo

Research Director
Leandro Ioshpe Zimerman

Assistance Quality Director
Walter José Gomes

Specialized Departments Director
João David de Sousa Neto

State and Regional Relations Director
José Luis Aziz

Cardiovascular Health Promotion Director - SBC/Funcor
Weimar Kunz Sebba Barroso de Souza

General Ombudsman
Lázaro Fernandes de Miranda

Chief Editor of the Brazilian Archives of Cardiology
Luiz Felipe Pinho Moreira

Governador - ACC Brazil Chapter
Roberto Kalil Filho

ADJUNCT COORDINATION

International Relations Coordinator
David de Pádua Brazil

Universidade Corporativa Coordinator
Gilson Soares Feitosa Filho

Standards and Guidelines Coordinator
José Francisco Kerr Saraiva

Cardiovascular Records Coordinator
Otávio Rizzi Coelho

Professional Valuation Coordinator
Carlos Japhet da Matta Albuquerque

New Projects Coordinator
Fernando Augusto Alves da Costa

Continuing Education Coordinator
Marcelo Westerlund Montera e Rui Manuel dos Santos Póvoa

Strategic Planning Concil
Andrea Araújo Brandão, Ari Timeman, Dalton Bertolin Precoma, Fábio Biscegli Jatene

SBC Newsletter Editor
Carlos Eduardo Suaide Silva

PRESIDENTS OF STATE AND REGIONAL BRAZILIAN SOCIETIES OF CARDIOLOGY

SBC/AL – Pedro Ferreira de Albuquerque
SBC/BA – Nivaldo Menezes Filgueiras Filho
SBC/CE – Sandro Salgueiro Rodrigues
SBC/CO – Danilo Oliveira de Arruda
SBC/DF – José Roberto de Mello Barreto Filho
SBC/ES – Bruno Moulin Machado
SBC/GO – Aguinaldo Figueiredo Freitas Jr.
SBC/MA – Márcio Mesquita Barbosa
SBC/MG – José Carlos da Costa Zanon
SBC/MS – Delcio Gonçalves da Silva Junior
SBC/MT – Max Wagner de Lima
SBC/NNE – Claudine Maria Alves Feio
SBC/PA – Sônia Conde Cristino
SBC/PE – Paulo Sérgio Rodrigues Oliveira
SBC/PB – Miguel Pereira Ribeiro
SBC/PI – Wildson de Castro Gonçalves Filho
SBC/PR – Gerson Luiz Bredt Júnior
SBC/RJ (SOCERJ) – Ricardo Mourilhe Rocha
SBC/RN – Maria de Fátima Azevedo
SBC/RO (SOCERON) – João Roberto Gemelli
SBC/RS (SOCERGS) – Gustavo Glotz de Lima
SBC/SC – Maria Emilia Lueneberg
SBC/SE – Sergio Costa Tavares Filho
SBC/SP (SOCESP) – Ibraim Masciarelli Francisco Pinto
SBC/TO – Andrés Gustavo Sánchez

DEPARTAMENTS AND STUDY GROUPS

SBC/DA – André Arpad Faludi
SBC/DCC – José Carlos Nicolau
SBC/DCC/CP – Maria Angélica Binotto
SBC/DCM – Elizabeth Regina Giunco Alexandre
SBC/DECAGE – José Maria Peixoto
SBC/DEIC – Luis Eduardo Paim Rohde
SBC/DERC – Salvador Manoel Serra
SBC/DFCVR – João Jackson Duarte
SBC/DHA – Eduardo Costa Duarte Barbosa
SBC/DIC – Samira Saady Morhy
SBCCV – Fabio Biscegli Jatene
SBHCI – Marcelo José de Carvalho Cantarelli
SOBRAC – Denise Tessariol Hachul
GAPO – Bruno Caramelli
GECC – Mauricio Wajngarten
GECESP – Daniel Jogaib Daher
GECETI – Gilson Soares Feitosa Filho
GECHOSP – Evandro Tinoco Mesquita
GECIP – Gisela Martina Bohns Meyer
GECN – Andréa Maria Gomes Marinho Falcão
GECO – Roberto Kalil Filho
GEECABE – José Antônio Marin Neto
GEECG – Nelson Samesima
GEICPED – Estela Azeka
GEMCA – Álvaro Avezum Junior
GEMIC – Felix Jose Alvarez Ramires
GERCPM – Tales de Carvalho
GERTC – Marcello Zapparoli
GETAC – João David de Souza Neto
GEVAL – Luiz Francisco Cardoso

Volume 30, Number 4, July/August 2017
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 - Gerência Científica - Núcleo de Publicações
MMM Design & Editoração

Former SOCERJ Magazine (ISSN 0104-0758) up to December 2009; Revista Brazileira 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 BrazilEIRA DE CARDIOLOGIA - SBC
PUBLICAÇÃO BIMESTRAL / PUBLISHED BIMONTHLY
INTERNATIONAL JOURNAL OF CARDIOVASCULAR SCIENCES
(INT J CARDIOVASC SCI)

This work is available per guidelines from the Creative Commons License. Attribution 4.0 International. Partial or total reproduction of this work is permitted upon citation.

The International Journal of Cardiovascular Sciences (ISSN 2359-4802)
bi-monthly edited by SBC:
Av. Marechal Câmara, 160 - 3º andar - Sala 330
20020-907 • Centro • Rio de Janeiro, RJ • Brazil
Telephone number: (21) 3478-2700
e-mail: **revistaijcs@cardiol.br**
<**www.onlineijcs.org**>

International Journal of Cardiovascular Sciences. 2017;30(4):283-284

EDITORIAL

Cardiology Journals from Portuguese-Speaking Countries: Challenges and Opportunities

Luiz Felipe P. Moreira

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

Scientific development is currently happening at an increasingly faster pace. With this situation, the scientific journals are required to commit to disseminating new knowledge with greater agility and broad propagation by the main international indexers. On the other hand, the mission of the scientific journals is also to encourage the propagation and discussion of new subjects in scientific communities, a situation of great importance mainly for those journals associated with medical societies and with a predominantly national circulation.

With respect to scientific propagation at an international level, the use of the English language has been well defined as being universal, leaving those publications in other languages to the background. Only articles published in English in broadly indexed journals achieve a greater number of citations, collaborating effectively in consolidating the involved research groups and elevating the impact of the periodicals in which they were published.[1] On the other hand, health professionals in several countries still encounter difficulties in accessing the international scientific literature and find in their local language the primary means to keep up with new knowledge.

According to the indexer SCImago, from the company Elsevier, Portuguese-speaking countries were responsible for more than 20 thousand scientific publications indexed in the health-related area in 2015.[2] Of these, 1130 were published in the areas of cardiology or cardiovascular sciences, representing 2.1% of all the publications in these areas of knowledge.[2] Most of these studies originated from Brazil or Portugal, countries that have consistently ranked among the 30 most important in the production of knowledge in health sciences over the past two decades. Among the publications from Portuguese-speaking countries, there is a predominance of publications in journals with international circulation, written in English, which have a greater potential for knowledge dissemination. However, about 42% of the studies from Brazilian or Portuguese researchers have been only published in Portuguese or in both languages, English and Portuguese, emphasizing the relevance of these publications for countries of Lusitanian culture. According to the SciELO portal, the number of views of articles published in Portuguese in the *Arquivos Brasileiros de Cardiologia*, a journal with articles indexed in the portal in both Portuguese and English, totaled more than 4.6 million downloads in 2016, while the number of downloads of publications in English of these same studies were slightly more than 2.9 million.[3] The greater number of views of articles in Portuguese both for original articles and articles focused on knowledge dissemination and discussion, clearly demonstrate the importance of maintaining the publications in our language for better access by our professionals.

Another important fact refers to the observation that the journals published by national societies concentrate mainly publications originating in their own countries, representing the main vehicle for the international dissemination of internally conducted research. In this sense, the *Arquivos Brasileiros de Cardiologia* continues to be the journal responsible for dissemination of approximately 25% of the Brazilian publications indexed in cardiology or cardiovascular sciences,[4] the same happening with the *Revista Portuguesa de Cardiologia* with regard to almost 30% of the publications from Portugal in these areas of knowledge. On the other hand, these journals are able to publish less than half of the currently submitted articles, limiting the appropriate dissemination

Keywords

Cardiovascular Diseases; Periodicals as Topic; Bibliometrics; Bilinguism.

Mailing Address: Luiz Felipe P. Moreira
Av. Dr. Enéas Carvalho Aguiar, 44, 2º andar, bloco 2, sala 13, Cerqueira César. Postal Code: 05403-000, São Paulo, SP – Brazil
E-mail: luiz.moreira@incor.usp.br

DOI: 10.5935/2359-4802.20170050

of studies by many researchers who find difficulties in accessing other means of publication.[4]

Based on these facts, scientific publications from countries with specific cultural characteristics, such as Portuguese-speaking ones, must be guided by policies that take into account both the need for wide dissemination of their contents at the international level, as well as their appropriate dissemination among members of their own professional community. With the increasing scientific research in cardiology and cardiovascular sciences in Portuguese-speaking countries in recent years, new opportunities have opened up for the expansion of our editorial activity. In this sense, the incorporation of the *International Journal of Cardiovascular Sciences* by the Brazilian Society of Cardiology, a journal published in English and Portuguese with a similar editorial quality as the *Arquivos Brasileiros de Cardiologia*, meets the conditions suitable for a greater international reach for the Brazilian cardiology science without neglecting a wide dissemination at the national level.[4]

References

1. Moreira LF. Impact of Brazilian papers in cardiology and cardiovascular sciences in the last decade. Arq Bras Cardiol. 2017;108(1):1-2.
2. SCImago. SJR - SCImago Journal & Country Rank. 2015. [Accessed in 2017 Apr 10]. Available from: http://www.scimagojr.com/countryrank.php?category=2705&area=2700&year=2015
3. Scielo. Métricas dos Arquivos Brasileiros de Cardiologia [Accessed in 2017 Apr 10]. Available from: http://www.scielo.br/statjournal.php?lang=pt&issn=0066-782X&collection=
4. Moreira LF. Role of the International Journal of Cardiovascular Sciences in the increase of Brazilian publications in Cardiology and Cardiovascular Sciences. Arq Bras Cardiol. 2016;107(1):1.

International Journal of Cardiovascular Sciences. 2017;30(4):285-292

ORIGINAL ARTICLE

24-Hour Ambulatory Blood Pressure Monitoring Predicts Outcomes of Hypertensive Patients in Primary Care: A Cohort Study

Guilherme Brasil Grezzana, Airton Tetelbon Stein, Lucia Campos Pellanda

Instituto de Cardiologia, Fundação Universitária de Cardiologia, Porto Alegre, RS – Brazil

Abstract

Background: Arterial hypertension is an important risk factor for cardiovascular outcomes. However, in most Primary Health Care centers, blood pressure remains at inadequate control levels. Ambulatory Blood Pressure Monitoring (ABPM) is a useful tool in predicting cardiovascular morbidity and mortality. The implementation of 24-hour ABPM and evaluation of cardiovascular outcomes in Primary Health Care may be effective in improving strategies for monitoring hypertensive patients in this setting.

Objective: To evaluate uncontrolled arterial hypertension detected by 24-hour ABPM as a predictor of cardiovascular outcomes in hypertensive patients from Primary Health Care in a low-resource environment.

Methods: Cohort study based on primary health care centers. The study was carried out with 143 hypertensive patients, who underwent 24-hour ABPM at baseline. Therapeutic targets were based on the Eighth Joint National Committee, the Brazilian Hypertension Guideline, and the European Hypertension Guideline. Medical records of emergency care, hospital admissions, and death certificates were reviewed.

Results: The sample consisted of 143 patients who met the inclusion criteria. After 4 years of follow-up, there were 17 deaths, 12 new cases of atrial fibrillation and 37 hospital admissions related to cardiovascular outcomes. During the follow-up period, the 24-hour ABPM showed a predictive result for new cases of atrial fibrillation ($p = 0.015$) and a combination of cardiovascular outcomes, mortality, and hospital admissions ($p = 0.012$).

Conclusion: The 24-hour ABPM was an important predictor of cardiovascular outcomes in a hypertensive population that seeks assistance in Primary Health Care centers. (Int J Cardiovasc Sci. 2017;30(4):285-292)

Keywords: Blood Pressure Monitoring, Ambulatory; Hypertension / complications; Public Health; Cardiovascular Diseases.

Introduction

Arterial hypertension is a major risk factor for cardiovascular disease.[1] Epidemiological studies have provided unequivocal evidence for the association between arterial hypertension and mortality from ischemic heart disease, cerebrovascular accident (CVA), and vascular diseases.[2] Additionally, there is a strong association between blood pressure (BP) reduction and prevention of coronary artery disease (CAD) and CVA.[3]

The number of individuals with uncontrolled hypertension (systolic BP ≥ 140 mmHg or diastolic BP ≥ 90 mmHg) increased from 605 to 978 million, among other causes, influenced by population aging.[4] The absolute increase of the hypertensive population should lead to an increase in the use of health services, which increases the need to identify and treat hypertension to prevent having to manage the costs of complications associated with the disease.[5]

The 24-hour ambulatory blood pressure monitoring (ABPM) is the most accurate tool to assess BP as a predictor of cardiovascular events, when compared to other methods, such as home and conventional BP measurements.[6] However, in the primary health care

Mailing Address: Guilherme Brasil Grezzana
Rua Oswaldo Hampe, 258. Postal Code: 95250-000, Centro, Antônio Prado, RS – Brazil
E-mail: gbgrezzana@bol.com.br, gbgrezzana@yahoo.com.br

DOI: 10.5935/2359-4802.20170061

Manuscript received November 01, 2016, revised manuscript February 01, 2017, accepted April 05, 2017.

(PHC) setting the availability and use of ABPM are below their indications, and general practitioners play a critical role in controlling hypertension.[7]

Several prospective studies have evaluated the predictive value of ABPM in relation to conventional BP measurement, such as the Dublin Outcome Study[8] and the International Database of Ambulatory Blood Pressure in relation to Cardiovascular Outcome (IDACO)[9], both with a significant follow-up time (8.4 and 9.5 years, respectively). Additionally, the CARDIORISC study,[10] with a sample size of 2,115 treated hypertensive patients, and a follow-up of 4 years, which included patients from the PHC setting, and national guidelines such as NICE[11] and CHEP,[12] recommend the ABPM method as a diagnostic tool for hypertension.

However, the diagnostic accuracy of hypertension based on conventional BP measurements is low,[13] and there is a scarcity in prospective studies evaluating the impact of 24-hour ABPM on hypertension control in PHC. In most PHC settings, 24-hour ABPM is still a scarcely used tool, and additional studies are needed to increase its implementation. The aim of the present study was to evaluate uncontrolled hypertension detected by 24-hour ABPM as a predictor of cardiovascular outcomes in hypertensive PHC patients in a low-resource setting.

Methods

Participants

This cohort study was based on PHC centers, including hypertensive patients from Antônio Prado (RS), a municipality in the Southern Region of Brazil, with a population of 12,883 inhabitants.[14] The samples were representative of the hypertensive patients who sought care at PHC centers in the municipality, being selected from a total of 646 patients registered in the system.

The inclusion criteria of the study were hypertensive patients, registered at the public health system participating in the hypertensive patient program and receiving regular pharmacological treatment in one of the two PHC centers of the municipality for at least 6 months.

From January 2009 to December 2010, the random sample of hypertensive patients was selected from the total set of hypertensive patients enrolled in two Basic Health Units, through the generation of random numbers using the program Microsoft Excel 2008.

Between January 2013 and October 2014, patients were invited to participate in the second phase of the study by telephone and/or by letter. Before being enrolled in this study phase, patients were reassessed by their PHC physicians. Patients who were not able to answer the questionnaire, pregnant women, those with electrocardiograms showing non-sinus rhythm, those who lived outside the coverage area of the PHC centers, those who moved to another city or were not contacted, and/or did not tolerate the use of ABPM, or had technical difficulty during the method application were excluded from the study.[13]

All patients who agreed to participate in the study signed the Free and Informed Consent form. The results obtained from the biochemical analyses and ABPM assessment during the study were delivered to the patients. The study was approved by the Research Ethics Committee of Instituto de Cardiologia do Rio Grande do Sul (protocol n. 4278.08).

Measurements

BP measurements were performed by the physicians of the PHC units. Three BP measurements were performed using a mercury sphygmomanometer – the use of the mercury sphygmomanometer is allowed in the State of Rio Grande do Sul, which follows the guidelines of the Collegiate Board Resolution n. 63-2011, Art. 23 – after being instructed to use appropriate-size cuffs.

Patients were in the sitting position, with their feet flat on the floor, and measurements were taken after at least 5 minutes of rest. PHC physicians were instructed to perform BP measurements on both arms, using as reference the highest BP value obtained after an interval of approximately 3 minutes. The first measurement was discarded, and the mean of the two subsequent measurements was considered and recorded in the patient's medical record.[7]

After this procedure, the patients were referred to the care of a nurse trained for the study for the 24-hour ABPM device placement, questionnaire application and anthropometric measurements. The collected data also included analysis of patients' medical records, request for biochemical exams, and assessment of ABPM data by the first author of the study, who was blinded to the BP assessment performed by the PHC physicians. The ABPM was performed during the patient's normal workday, with weekends and holidays being excluded from the analysis.

The ABPM monitors used in the study were adequately validated and calibrated according to international recommendations.[15] The ABPM recorder used was the DMS Brasil, TM 2430 model and the mercury sphygmomanometer used in the study was the MDF 800 model. The ABPM recordings were programmed to perform a BP measurement every 15 minutes during the waking period and every 30 minutes during sleep. The sleep and waking periods were individualized according to each patient's habits.

Data were considered adequate when at least 60 recordings were performed during the 24-hour period, with at least two recordings every hour during sleep. The parameters assessed by ABPM were the mean systolic and diastolic BP of the 24-hour period, during the waking and sleep periods. Uncontrolled hypertension, consistent with conventional sphygmomanometer criteria was defined, according to the main hypertension guidelines, as BP values ≥ 140 / 90 mmHg.[7]

For uncontrolled hypertension, ABPM criteria were used according to the European Hypertension Guideline and the Brazilian Society of Cardiology Guideline.[5,16] Thus, hypertensive patients with a mean 24-hour BP ≥ 130/80 mmHg, ≥ 135/85 mmHg in the waking period, and ≥ 120/70 for the mean nocturnal BP measurement for the first criterion were considered uncontrolled. [5] When the Brazilian Hypertension Guidelines were considered,[16] the BP values used in the study were the borderline values considered normal as cutoff values for the 24-hour means: > 125/75 mmHg, > 130/85 mmHg for the waking period and > 110/70 mmHg for the mean BP during sleep.

The absence of nocturnal dipping was defined as the decrease in BP by ABPM ≤ 10% in relation to the diurnal mean BP value.[16] The guidelines of the Eighth Joint National Committee[17] were also adapted for the group of patients aged 60 years and older.

In addition to the conventional BP measurement and 24-hour ABPM assessment, the patients' biochemical profile was also evaluated considering the following items: total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, creatinine, Glycated Hemoglobin A1c (HbA1c), microalbuminuria in a sample and fasting glycemia. Microalbuminuria measurement in a sample was expressed by the albumin/creatinine ratio. Anthropometric data, such as muscle mass, weight, waist-to-hip ratio, and body mass index, were also evaluated. The assessment also included validated tools to estimate smoking/nicotine dependence (Fagerström Test), Alcohol Use Disorder Identification Test (AUDIT) and the self-reported scale, indicating adherence to the proposed treatment (Morisky).[13] All tests performed, both ABPM and biochemical exams were made available to patients and their PHC physicians.

The death certificates and medical records were reviewed to verify the cardiovascular diseases identified in patients who sought medical care in the PHC network during the study period. Data were also collected in the emergency service of the referral hospital of the municipality. A 12-lead electrocardiogram was performed to confirm new diagnoses of atrial fibrillation reported by the PHC physicians, as well as in patients who showed an irregular heart rhythm during the 24-hour ABPM assessment.

Data Analysis

Data were analyzed using the Statistical Package for Social Sciences (SPSS), version 21.0. Descriptive statistics were calculated using continuous and categorical variables. Considering the sample size, the Kolmogorov-Smirnov test was used to verify data normality. Continuous variables with normal distribution were shown as mean and standard deviation, and the categorical variables, as absolute numbers and percentages. Comparison between the subgroups was performed using the Chi-square test, Mann Whitney U-test (continuous variables with non-homogeneous variance) and t-test (variables with homogeneous variances). Student's t-test was used to compare two paired samples, the same subjects at two different times. Median and interquartile range values were used for continuous variables with non-normal distribution. Kaplan-Meier analysis was used for survival analysis calculation. The confidence interval was set at 95% with 80% power. The estimated sample size was 143 patients and the level of statistical significance was set at 5%.

Results

From January 2013 to October 2014, data from a sample of 143 hypertensive patients, with a mean follow-up period of 3 years and 8 months, were collected and evaluated from a previous cross-sectional study sample (standard deviation 0.27 = 3.77 ± 0.27)[13]. Of this sample, 16 patients were not located and nine dropped out of the

study protocol, although they did not report any clinical outcome before leaving the study during this period. There were 17 deaths and, thus, 101 hypertensive patients were included in the follow-up registry (flow chart).

The analyzed sample consisted predominantly of female patients (65.3%), Caucasians (77.2%), mean age of 61.7 years (standard deviation ± 13.43). The prevalence of type 2 diabetes mellitus was 19%, dyslipidemia was 41%, and 36% of the study sample had microalbuminuria. Table 1 summarizes the patients' demographic profile and lifestyle. All patients had used antihypertensive medication for at least 6 months, with diuretics (77.3%) and angiotensin-converting enzyme inhibitors (60.4%) being the most often prescribed medications.

Table 1 – Demographic analysis and lifestyle

Variables	Cohort*
Female gender, n (%)	66 (65.3%)
Age, years	61.72 ± 13.43 (25-89)
Caucasian ethnicity	78 (77.2%)
Body mass index	28.52 ± 4.58 (20-44)
Fasting glucose, mg/dL	98.97 ± 25.64 (65-211)
Glycated hemoglobin A1c	5.95 ± 0.67 (5-8.6)
Total cholesterol, mg/dL	196.65 ± 39.19 (88 -354)
HDL, mg/dL	53.06 ± 11.47 (30-84)
LDL, mg/dL	115.6 ± 31.75 (33-189)
Triglycerides, mg/dL	154.83 ± 119.54 (36-1015)
Creatinine, mg/dL	0.91 ± 0.34 (0.42-3.09)
Smoking	6.9%
Alcohol (> 2 u/day)	27.7%
Microalbuminuria, > 30 mg/dL	36%
Physical activity, > 150 minutes/week)	56%

** Standard deviation, percentage, and maximum and minimum values.*

After 3 years of follow-up, 56 cardiovascular outcomes were identified (14 deaths, 11 new cases of atrial fibrillation and 31 hospital admissions secondary to cardiovascular causes, such as heart failure and acute myocardial infarction). After 4 years of follow-up, three deaths, one new case of atrial fibrillation and six hospital admissions were identified and added to the outcomes observed in the study. Thus, there were a total of 17 deaths (two from heart failure, four from CVA, seven from CAD, one from sepsis, one from bronchopulmonary carcinoma, one of multiple organ failure and one from pneumonia), 12 new cases of atrial fibrillation and 37 hospital admissions secondary to cardiovascular causes.

In the endpoints identified after 3 years of follow-up, uncontrolled BP evaluated by 24-hour ABPM was an independent predictor for new cases of atrial fibrillation (p = 0.029) (Table 2). After 4 years of follow-up, 24-hour ABPM was a risk predictor for new cases of atrial fibrillation (p = 0.015) and combined cardiovascular outcomes (p = 0.012) (Table 3). Thus, at the end of the third year of follow-up, there were 77.8% (p = 0.092) of the total outcomes considering the BP group not controlled by ABPM and 79.7% (p = 0.012) at the end of the fourth year of follow-up (Table 4). In the survival analysis, the mean time until the event was 32.5 months (95% Confidence Interval - 95% CI: 30.4 - 34.7).

Discussion

The main outcome of this contemporary cohort study evaluating hypertensive patients coming from the PHC setting is that 24-hour ABPM is a predictor for cardiovascular outcomes at this level of health care. Moreover, many of these patients were considered as having uncontrolled BP when they were reclassified according to the BP means using the 24 hour-ABPM after a mean period of 3 years and 8 months of follow-up.[8] These findings allow some interpretations when considering the control of cardiovascular risk factors and the most appropriate use of diagnostic tools in the hypertensive population treated at the PHC level. There is evidence that 24-hour ABPM can be considered a useful tool in the PHC scenario, being used to improve cardiovascular risk stratification in hypertensive patients at the PHC level.[18]

Ohkubo et al.[19] observed a correlation between BP levels obtained from ABPM and mortality. Large and significant prospective studies have demonstrated that ABPM is a better predictor of future cardiovascular events when compared to conventional BP measurements obtained in the medical office.[8,9,20] The 24-hour ABPM is a tool capable of predicting cardiovascular outcomes in the long-term with odds ratios ranging from 1.28 to 1.4,[15] being the only BP measurement strategy with such capacity.[6] Therefore, based on the prognostic evidence, ABPM was selected as the reference standard for BP measurements and to assess the diagnostic accuracy of conventional BP measurements.[15]

Table 2 – Cardiovascular outcomes after 3 years of follow-up through 24-hour ambulatory blood pressure monitoring (ABPM)

Outcome	Controlled BP (%)	Uncontrolled BP (%)	*p* value*
Death	7.7	19.1	0.216
AF	0	17.7	0.029
Combined outcomes†	46.2	67.7	0.92

** Chi-square; †death, atrial fibrillation, and hospital admission; BP: blood pressure; AF: atrial fibrillation.*

Table 3 – Cardiovascular outcomes after 4 years of follow-up through 24-hour ambulatory blood pressure monitoring (ABPM)

Outcome	Controlled BP (%)	Uncontrolled BP (%)	*p* value*
Death	7.7	22.6	0.134
AF	0	19.4	0.015
Combined outcomes†	46.2	75.8	0.012

** Chi-square; †death, atrial fibrillation, and hospital admission; BP: blood pressure; AF: atrial fibrillation.*

Table 4 – Combined cardiovascular outcomes (death, atrial fibrillation and hospital admission) after 4 years of follow-up assessed by conventional blood pressure (BP) measurement and 24-hour ambulatory BP monitoring (ABPM)

Uncontrolled BP	Outcome		*p* value
	Present (%)	Absent (%)	
Uncontrolled BP at ABPM	79,7	24,2	0,012
Uncontrolled BP at conventional BP measurement	54,5	45,5	0,064

In the present cohort study, we expected to find a population of hypertensive patients with low to intermediate cardiovascular risk, as the entire sample consisted of patients from PHC. However, most of the patients were classified as intermediate to high risk for cardiovascular outcomes, due to the findings of type 2 diabetes, dyslipidemia, and microalbuminuria in the assessed sample. Such findings are probably due to the fact that the municipality where the study was carried out does not have a tertiary care center and, thus, most patients are treated in these PHC centers, regardless of their basal pathological condition. This aspect, in the care of the hypertensive patient, could justify the significant number of cardiovascular outcomes including mortality, new cases of atrial fibrillation and hospital admissions, being the same predicted by the uncontrolled BP assessment by 24 hour-ABPM. Conversely, when compared with conventional BP measures, a reverse causality of outcomes was observed. Thus, ABPM was a better predictor of cardiovascular outcomes in hypertensive patients, when compared to conventional BP measurements. These findings agree with previous studies that analyzed the relative risk of cardiovascular outcomes associated with the mean nocturnal and 24-hour BP measurements. [21]

The innovative aspect of the present study is the fact that the sample was obtained from a population originated exclusively from PHC, where most arterial hypertension diagnoses and treatment are performed.[22] The patients had a high mortality rate (17 deaths in a total of 143 patients in 3.5 years of follow-up) compared to other studies, such as the TASMINH 3 Trial,[23] of high-risk UK patients in PHC, randomized to BP self-measurement or control, in which two deaths were observed in a sample of 555 patients with a follow-up period of approximately two years. Moreover, no death was reported in the TASMINH Trial 2[24], which had a similar sample size to the previously mentioned one, with a 1-year follow-up. The differences in mortality rates could reflect the impact of several care strategies used with hypertensive patients, as well as differences in cardiovascular risk in the assessed populations. Thus, the broad use of health technologies, such as ABPM in this context, could be used as an auditing tool for the public health system quality assessment.

In a recent meta-analysis, it was observed that a large part of the cardiovascular risk obtained from the 24-hour BP assessment could be explained by the reduction in the nocturnal dipping, with a significant cardiovascular risk excess of 27% in relation to the normal nocturnal dipping pattern during sleep.[18] When considering only the nocturnal BP mean, 63.3% of the assessed patients did not have nocturnal dipping, which may have contributed to the observed outcomes. This prevalence is similar to that found in other studies, in which the absence of nocturnal dipping ranged from 60 to 67.5%.[25]

However, these studies were carried out in different health care settings, which did not incorporate PHC. Masked hypertension could be pointed out as another factor contributing to the high number of outcomes observed in the study. The prevalence of masked hypertension in the study ranged from 46.9 to 56.1%, considering the different thresholds for the ABPM targets used in the study. Additionally, there is an association between target-organ lesions in patients with masked hypertension and unfavorable cardiovascular prognosis.[26,27]

Arterial hypertension is a risk factor for new cases of atrial fibrillation due to left atrial overload and subsequent arrhythmia.[22] However, this study identified that the mean age of patients who developed atrial fibrillation was 63.6 years, consisting of another risk factor for new cases of atrial fibrillation.[28] Additionally, mortality due to CAD and CVA can show a 3-fold increase with each increase of 10 years in age, demonstrating the importance of adequate BP control in reducing cardiovascular risk over the years.[29]

The ABPM can provide prognostic information in terms of cardiovascular risk, contributing to treatment from the 24-hour BP assessment and antihypertensive treatment optimization.[30] These benefits are inherent to 24-hour BP and have been shown to be associated with a reduction in hospital admissions from cardiovascular disease and death in patients seeking medical care at PHC centers. Moreover, the routine use of ABPM in BP assessment may prevent the unnecessary treatment of hypertensive patients with white-coat effect and masked hypertension,[26] thus contributing to the cost-effectiveness of arterial hypertension management at the PHC level.[31]

In a relatively short period of time, a significant number of hospital admissions from cardiovascular causes was observed, and this was a relevant finding of this study. When considering the impact of patient reclassification according to the different thresholds of normality for ABPM and the conventional BP measurement, the diagnostic accuracy of the conventional BP assessment performed at the PHC centers was low, regardless of the method used. Therefore, the 24-hour ABPM resulted in the auditing of the care provided at the PHC centers, based on the incidence of cardiovascular outcomes observed, and the association with low BP control. These findings can contribute to the development of new hypertensive patient care strategies in the PHC setting.

Sample size may be considered a limitation of the present study. However, considering the high number of cardiovascular outcomes observed in the relative short period of time, the sample calculation based on a previous study with the same population base,[13] the absence of PHC service offered by the private network and the population size, the present study power was adequate for the study aim. The sample, consisting of patients with chronic pathological conditions and having PHC as the highest reference in detriment to the availability of secondary and tertiary health care, may have contributed to the important number of outcomes observed. Therefore, the use of ABPM as a predictive tool for cardiovascular outcomes in a sample obtained exclusively from PHC centers provides some perspectives for the development of preventive strategies for patients whose clinical profile is similar to that of the studied sample.

Conclusion

A large number of hospital admissions and cardiovascular events were identified in a cohort of hypertensive patients who sought medical assistance in Primary Health Care centers. The 24-hour ABPM showed adequate predictive capacity for cardiovascular outcomes when compared to conventional BP measurements. This study suggests the need for reassessment of preventive strategies in PHC centers, especially considering the care of the hypertensive patient. The 24-hour ABPM can be considered a good tool for assessing BP measurements and could be useful in the management of BP control in hypertensive patients and as a predictor of cardiovascular outcomes in the Primary Health Care setting.

Author contributions

Conception and design of the research: Grezzana GB, Stein AT, Pellanda LC. Acquisition of data: Grezzana GB. Analysis and interpretation of the data: Grezzana GB, Stein AT, Pellanda LC. Statistical analysis: Grezzana GB. Obtaining financing: Grezzana GB. Writing of the manuscript: Grezzana GB, Stein AT, Pellanda LC. Critical revision of the manuscript for intellectual content: Grezzana GB, Stein AT, Pellanda LC.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by first author.

Study Association

This article is part of the thesis of Doctoral submitted by Guilherme Brasil Grezzana, from Instituto de Cardiologia do Rio Grande do Sul - ICFUC.

References

1. Fuchs FD, Fuchs SC, Moreira LB, Gus M. Proof of concept in cardiovascular risk: the paradoxical findings in blood pressure and lipid abnormalities. Vasc Health Risk Manag. 2012;8:437-42.
2. Pessanha P, Viana M, Ferreira P, Bertoquini S, Polónia J. Diagnostic value and cost-benefit analysis of 24 hours ambulatory blood pressure monitoring in primary care in Portugal. BMC Cardiovasc Dis. 2013:13:57.
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;338:b1665.
4. Lim SS, Vos T, Flaxman AD, Danari G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012;380(9859):2224-60.
5. Murphy CM, Kearney PM, Shelley EB, Fahey T, Dooley C, Kenny RA. Hypertension prevalence, awareness, treatment and control in the over 50s in Ireland: evidence from The Irish Longitudinal Study on Ageing. J Public Health. 2016;38(3):450-8.
6. Niiranen T, Maki J, Puukka P, Karanko H, Jula AM. Office, home, and ambulatory blood pressure as predictors of cardiovascular risk. Hypertension. 2014;64(2):281-6.
7. Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al; Task Force Members. 2013 ESH/ESC Guidelines for the management of arterial hypertension. The Task Force for the management of arterial hypertension of the European Society of Hypertesnion (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013;31(7):1281-357.
8. Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, et al. Superiority of ambulatory over clinic blood pressure measurement ini predicting mortality: the Dublin outcome study. Hypertension. 2005;46(1):156-61.
9. Hansen TW, Kikuya M, Thijs L, Bjorklund-Bodegard K, Kuznetosova T, Ohkubo T, et al. Prognostic superiority of daytime ambulatory over conventional blood pressure in four populations: a meta-analysis of 7,030 individuals. J Hypertens. 2007;25(8):1554-64.
10. de la Sierra A, Banegas JR, Seugra J, Gorostidi M, Ruilope LM, CARDIORISC Event Investigators. Ambulatory blood pressure monitoring and development of cardiovascular events in high-risk patients included in the Spanish ABPM registry: the CARDIORISC Event study. J. Hypertens. 2012;30(4):713-9.
11. NICE Clinical Guideline 127 Developed by the Newcastle Guideline Development and Research Unit and updated by the National Clinical Guideline Centre (formerly the National Collaborating Centre for Chronic Conditions) and The British Hypertension Society. [Cited in 2016 Jun 10]. Available from: http://www.nice.org.uk/guidance
12. Campbell NR, Kaczorowski J, Lewanczuk RZ, Feldman R, Poirier L, Kwong MM, et al; Canadian Hypertension Education Program. 2010 Canadian Hypertension Education Program (CHEP) recommendations: the scientific summary - an update of the 2010 theme and the science behind new CHEP recommendations. Can J Cardiol. 2010;26(5):236-40.
13. Grezzana GB, Stein AT, Pellanda LC. Blood pressure treatment adherence and control through 24-hour ambulatory monitoring. Arq Bras Cardiol. 2013;100(4):335-61.
14. Instituto Brasileiro de Geografia e Estatística. (IBGE). Cidades@. Rio Grande do Sul – Antonio Prado. [Citado em 2015 jun 10]. Disponível em http://www.cidades.ibge.gob.br/xtras/perfil.php?lang=&codmun=430080&search=rio-grande-do-sul/antonio-prado
15. Piper MA, Evans CV, Burda BU, Margolis KL, O'Connor E, Whitlock EP. Diagnostic and predictive accuracy of blood pressure screening methods with consideration of rescreening intervals: an updated systematic review for the U.S. preventive services task force. Ann Intern Med. 2015;162(3):192-204.

16. Malachias MV, Souza WK, Plavnik FL, Rodrigues CI, Brandão AA, Neves MF, et al; Sociedade Brasileira de Cardiologia. 7a Diretriz Brasileira de hipertensão arterial. Arq Bras Cardiol. 2016;107(3 supl 3):1-83.

17. James PA, Oparil S, Carter BL, Cushman WC, Dennison-Himmelfarb C, Handler J, et al. 2014 Evidence-based guideline for the management of high blood pressure in adults: report the panel members appointed to the eighth Joint National Committee (JNC 8). JAMA. 2014;311(5):507-20. Erratum in: JAMA. 2014;311(17):1809.

18. Salles GF, Reboldi G, Fagard RH, Cardoso CR, Pierdomenico SD, Verdecchia P, et al; ABC-H Investigators. Prognostic effect of the nocturnal blood pressure fall in hypertensive patients: the Ambulatory Blood Pressure Collaboration in Patients With Hypertension (ABC – H) meta-analysis. Hypertension. 2016;67(4):693-700.

19. Ohkubo T, Imai Y, Tsuji I, Nagai K, Watanabe N, Minami N, et al. Prediction of mortality by ambulatory blood pressure monitoring versus screening blood pressure measurements: a pilot study in Ohasama. J Hypertens. 1997;15(4):35-64.

20. Bendzala M, Kruzliak P, Gaspar L, Soucek M, Mrdovic I, Sabaka P, et al. Prognostic significance of dipping in older hypertensive patients. Blood Press. 2015;24(2):103-10.

21. Conen D, Bamberg F. "Noninvasive 24-h ambulatory blood pressure and cardiovascular disease: a systematic review and meta-analysis." J Hypertens. 2008;26(7):1290-9.

22. Filippi A, Sangiorgi D, Buda S, Degli Esposti L, Nati G, Paolini I, et al. How many hypertensive patients can be controlled in "real life": an improvement strategy in primary care. BMC Fam Pract. 2013;14:192.

23. Primary Care Health Sciences. Nufffiel Departament of Medical Sciences Divison. [Cited in 2016 Nov 15]. Available from: https://www.phc.ox.ac.uk

24. McManus RJ, Mant J, Bray EP, Holder R, Jones MI, Greenfield S, et al. Telemonitoring and self-management in control of hypertension (TASMINH2): a randomised controlled trial. Lancet. 2010;376(9736):163-72.

25. Kaya MG, Yarlioglues M, Gunebakmaz O, Gunturk E, Inanc T, Dogan A, et al. Platelet activation and inflammatory response in patients with non-dipper hypertension. Atherosclerosis. 2010;209(1):278-82.

26. Cuspidi C, Sala C, Tadic M, Rescaldani M, Grassi G, Mancia G. Untreated masked hypertension and subclinical cardiac damage: a systematic review and meta-analysis. Am J Hypertens. 2015;28(6):806-13.

27. Sattur S, Sarwar B, Sacchi TJ, Brenner SJ. Correlation between markers of reperfusion and mortality in ST-elevation myocardial infarction: a systematic review. J Invasive Cardiol. 2014;26(11):587-95.

28. Ieraci L, Park-Wyllie L; Health Quality Ontario. Twenty-four-hour ambulatory blood pressure monitoring in hypertension: an evidence-based analysis. Ont Health Technol Assess Ser. 2012;12 (15):1-65.

29. 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;338:b1665.

30. Hodgkinson J, Mant J, Martin U, Guo B, Hobbs FD, Deeks JJ, et al. Relative effectiveness of clinic and home blood pressure monitoring compared with ambulatory blood pressure monitoring in diagnosis of hypertension: systematic review. BMJ. 2011;342:d3621.

31. Nascimento LR, Molina MCB, Faria CP, Cunha RdeS, Mill JG. Reproducibility of arterial pressure measured in the ELSA-Brasil with 24-hour pressure monitoring. Rev Saude Publica. 2013;47(Suppl 2):113-21.

International Journal of Cardiovascular Sciences. 2017;30(4):293-298

ORIGINAL ARTICLE

Are Patients' Blood Pressure Levels Being Routinely Measured in Medical Offices?

Israel Guilharde Maynarde, Thiago Veiga Jardim, Weimar Kunz Sebba Barroso de Souza, Ana Luiza Lima Sousa, Andrey Rocha Rocca, Bruna Yana de Carvalho Lin, Natália Mirelle Carrijo dos Santos, Diogo Pereira Santos Sampaio, Xênia Larissa Motta Serafim, Paulo Cesar Brandao Veiga Jardim

Liga de Hipertensão – Universidade Federal de Goiás (UFG), Goiânia, GO – Brazil

Abstract

Background: Blood pressure measurement is recommended in all medical evaluations, regardless of the specialty. It is a simple and easy-to-do procedure, but usually neglected or performed incorrectly.

Objectives: To assess if blood pressure is being measured routinely and compare the values obtained in the usual ambulatory consultations to those obtained when following the adequate techniques.

Methods: Cross-sectional and observational study that included adult (age >18 years) outpatients treated in clinical and surgical specialties of a teaching hospital. Subjects answered a specific questionnaire and then three blood pressure measurements were performed according to the current guidelines by trained research staff. After that, the patients had their appointments and at the end, the medical charts were checked to see if blood pressure was measured and, if so, the observed value was recorded.

Results: We included 129 consecutive patients with a mean age of 53 years (± 15.92) predominantly females (61.2%). Most of the appointments occurred in clinical specialties (70.5%) and 49.6% reported themselves as hypertensive. Blood pressure was not measured in 38.8% of the patients, more frequently in surgical specialties (72,5% vs. 27,5%; p < 0,001). The previous diagnosis of hypertension did not influence the chance of a patient having his blood pressure measured (p = 0,082). There were no differences between the blood pressure measured by the researchers and those recorded at the medical charts (118 mmHg vs. 117 mmHg; p = 0,651; 72 mmHg vs. 75 mmHg; p = 0,055).

Conclusions: The patients' blood pressure levels were not measured in many of the medical appointments, especially at outpatient clinics of surgical specialties. (Int J Cardiovasc Sci. 2017;30(4):293-298)

Keywords: Blood Pressure; Outpatient Service; Ambulatory Care; Hypertension; Physician's Offices.

Introduction

Systemic Arterial Hypertension (SAH) is, by definition, diagnosed by the detection of high and sustained levels of Blood Pressure (BP) obtained during a casual measurement.[1] Additionally, much of the knowledge about such a prevalent condition derives from observational and/or intervention data obtained at the approach of hypertensive patients acquired with the use of casual BP measurement.[2]

Although some guidelines that address the SAH topic suggest the superiority of the Ambulatory Blood Pressure Measurement (ABPM) in relation to outpatient measures for the disease diagnosis,[1-4] the casual BP measurement is recommended in any medical assessment, regardless of the specialty.[1,2,4] It consists of a simple and easy to perform procedure, but it is often performed inadequately.[1]

The indirect manual measurement techniques, available and disseminated in our country, are the auscultatory (mercury or aneroid column sphygmomanometers) and oscillometric techniques using semi-automatic devices.

The problems of manual measurements at the office result from factors such as the use of inadequate or uncalibrated devices,[5-7] measurements that do not

Mailing Address: Thiago Veiga Jardim
Faculdade de Medicina, Universidade Federal de Goiás, 1ª Avenida s/n, Setor Leste Universitário. Postal Code: 74605-020, Goiânia, GO – Brazil
E-mail: thiagoveiga@cardiol.br

DOI: 10.5935/2359-4802.20170055

Manuscript received July 19, 2016, revised manuscript November 21, 2016, accepted February 20, 2017.

follow the protocol adequately, by applying inadequate techniques,[8] the white coat effect,[9,10] the rounding of the values found[11] and intraobserver variations.[12]

In addition to these situations, there is also a growing concern about the non-routine performance of BP measurement by health professionals. This fact implies serious problems in hypertension diagnosis, since it is an oligo- or asymptomatic condition, for which BP measurement is the only available tool for establishing the diagnosis.[1-4]

Therefore, it becomes increasingly more important to study BP measurement techniques routinely used in our health services, focusing both on the technical aspect of the measurement and on its performance. With this objective, we analyzed whether BP measurement was routinely being carried out in outpatient settings of a school hospital. Moreover, we compared the values of the BP measured in the waiting room, using the correct technique according to recommendations of guidelines,[1-4] by trained researchers, with the values obtained by the measurements performed at the offices by the professionals responsible for patient care.

Methods

This is a cross-sectional, observational and non-intervention study, carried out in adult patients (age > 18 years) treated at the outpatient (internal medicine, cardiology, pneumology, rheumatology, gastroenterology, nephrology, hematology, and endocrinology) and surgical (general surgery, coloproctology, urology, vascular and thoracic surgery) clinics of a university tertiary hospital.

The project was approved by the Research Ethics Committee of the institution and followed the guidelines of Resolution 466/2012 of the National Health Council. Before signing the Free and Informed Consent Form (FICF) and data collection, all subjects were informed of the study purpose and the procedures they would undergo, in addition to possible risks.

Sample size calculation, considering a previous publication[13] on the subject, which showed that approximately 60% of the patients did not have their BP measured, and considering an absolute precision of 10%, with a significance level of 5%, was of at least 92 patients.

Patients treated at the aforementioned outpatient clinics that filled out the FICF were consecutively included in the study, and those who were not able to answer the formulated questions and/or those who did not wish to undergo BP measurements were excluded.

Data were collected between October and December 2015 by three teams consisting of two previously trained researchers. The data were obtained during the consultations in the outpatient and surgical specialty clinics, in the morning or in the afternoon.

A questionnaire was created to collect anthropometric and clinical data from the patients, such as age (in full years), gender, self-reported ethnicity, and presence or absence of a previous hypertension diagnosis (according to the patient's self-reporting, without confirmation in medical records).

The study subjects, immediately before entering the office for the consultation, were submitted to three BP measurements with a validated and calibrated device (Omron Hem 7200 semi-automatic; Kyoto, Japan), with an interval of at least 1 minute between them, according to the recommendation of the VI Brazilian Hypertension Guidelines.[1] After the consultation, the medical record was checked to verify whether the BP was measured and, when it had been measured, this value was documented, as recorded in the medical file.

Statistical analysis

The data were stored in a database, created using Microsoft Excel™ and analyzed comparatively. Statistical analysis was performed using the software Statistical Package for Social Sciences (SPSS), version 21.0 (Chicago, IL, USA). The Kolmogorov-Smirnov test was used to verify the normality of data and confirmed that the continuous variables had a normal distribution. Student's *t*-test for paired samples was used to compare continuous study variables, expressed as mean and standard deviation. The comparative analysis between the categorical variable measurement or not of the BP was performed using the chi-square test. Values of $p < 0.05$ were considered significant.

Results

A total of 129 patients treated at local outpatient clinics were consecutively selected, 91 (70.5%) from clinical specialties and 38 (29.5%) from surgical specialties. Patient age ranged from 18 to 88 years, with a mean of 53 years (± 15.92). Most of the individuals (61.2%) were female and 49.6% reported a previous diagnosis of hypertension (Table 1).

Table 1 – General characteristics of patients

Characteristic	n (%)
Female gender	79 (61.2)
Ethnicity	
Black	12 (9.3)
White	63 (48.8)
Mixed-race	54 (41.9)
Previous systemic arterial hypertension	
Yes	64 (49.6)
No	65 (50.4)
Outpatient clinic specialty	
Clinical	91 (70.5)
Surgical	38 (29.5)

The number of patients in which the BP measurement was not performed was very significant (38.8%), with an even higher percentage of non-BP measurement in outpatient clinics of surgical specialties (Table 2).

Table 2 – Patient description regarding blood pressure (BP) measurement in clinical and surgical specialty consultations

Outpatient clinic specialty	BP measurement		p value*
	Yes n (%)	No n (%)	
Clinical	66 (72.5)	25 (27.5)	< 0.001
Surgical	13 (34.2)	25 (65.8)	

** Significant chi-square test at p < 0.05.*

When the previous diagnosis of SAH was compared with the BP measurement, there was no statistically significant difference (Table 3).

As a strategy to evaluate the real need to recommend that the pressure be measured three times at the consultation and consider the mean of the last two as the final measure, the BP at the first measurement was compared with the mean BP of the last two (Table 4).

The mean values of the last two BP measurements were also compared with the BP measured at the consultation and recorded in the file, with the purpose of evaluating the quality of the measurements performed in the outpatient clinics (Table 5).

Table 3 – Distribution of patients regarding the previous diagnosis of systemic arterial hypertension (SAH) and recording of blood pressure (BP) levels in medical files

Previous SAH	BP recording in medical files		p value*	Total
	Yes n (%)	No n (%)		
Yes	44 (68.8)	20 (31.2)	0.082	64
No	35 (53.8)	30 (46.2)		65

** Significant chi-square test at p < 0.05.*

Discussion

The BP measurement in all consultations, regardless of the medical specialty, is a current recommendation of most national1 and international guidelines[2-4] that address the SAH topic. In spite of this fact, the data found in the present study show that, even in a tertiary referral service, together with the special characteristic of being a school hospital, this recommendation was not followed by professionals in 38.8% of the consultations.

This fact becomes even more alarming when we compare the clinical and surgical specialties. In this case, there was a statistically significant difference between the number of patients in whom the pressure was not measured in the surgical specialty outpatient clinics when compared to the clinical specialties.

Although there is a great deal of data assessing BP measurement techniques,[14-20] few studies have assessed whether the measurement was actually performed.[13,21,22] There is also a marked difference between the studies published on the subject. Most of them used the BP measurement information reported by the physician, finding, with this methodology, percentages of BP measurement between 85 and 97%.[21,22] However, only one study[13] effectively verified whether BP was being measured, with data closer to those found in the present study. This study[13] analyzed 500 medical records and found annotation of BP values in only 39% of the consultations. This value is even lower than the 61.2% of measurement records we found; however, closer if

Table 4 – Comparison between the first measurement of systolic blood pressure (SBP) and diastolic blood pressure (DBP) with the arithmetic mean of the last two measurements

Variable	First measurement (mmHg)	Mean of the last two measurements (mmHg)	p value*
SBP, mean (SD)	121.56 (± 18.99)	119.04 (± 18.03)	< 0.001
DBP, mean (SD)	73.64 (± 12.12)	73.11 (± 11.55)	0.269

** Student's t test – significant at p < 0.05. SD: standard deviation.*

Table 5 – Comparison between the arithmetic mean of the last two measurements of systolic blood pressure (SBP) and diastolic blood pressure (DBP) with the values recorded in the medical files

Variable	Mean of the last two measurements	Recorded blood pressure	p value*
SBP, mean (SD)	118.70 (± 18.57)	117.89 (± 16.72)	0.651
DBP, mean (SD)	72.76 (± 11.16)	75.20 (± 10.80)	0.055

** Student's t test – significant at p < 0.05. SD: standard deviation.*

we consider only the surgical specialties, in which only 34.2% of the consultations had the results of BP values.

Another finding that is worth mentioning is the fact that the previous diagnosis of SAH did not positively influence BP measurement at the medical office. In the aforementioned study of Alavarce,[13] the previous diagnosis of SAH seemed to influence BP measurement (79% of hypertensive patients with BP measured at the consultation vs. 46% among non-hypertensive patients), a fact not reproduced with statistical significance in our findings. These data indicate a greater need for publications on the subject, which would enable the improvement of knowledge, defining whether the fact that the individuals are previously known to be hypertensive increases or not the chance of having their BP checked during a medical appointment.

There was also a statistically significant difference when comparing the mean of the last two measurements performed by the investigators with the first measurement of its systolic component alone, but not the diastolic component. This difference, even if significant only for the systolic component, is in agreement with the recommendation of the VI Brazilian Hypertension Guidelines,[1] as well as most of the international guidelines on SAH,[2-4] to perform at least three BP measurements at each consultation, considering the mean of the last two measures as final value. This strategy has been extensively assessed,[17,23-25] and has shown to be efficient in determining the most accurate BP of patients undergoing outpatient care and should always be reinforced.

The BP values collected by the researchers followed the correct calibration technique and considered as the final value the mean of the last two measures. Nonetheless, when compared to the consultation environment, they did not differ in the systolic, or in the diastolic component. A possible explanation is the fact that the patients were treated at a school-hospital, which would hypothetically favor the correct BP measurement. However, as the researchers did not participate in the consultations, we cannot affirm that the values recorded in the medical record were the result of an isolated measurement or of more than one measurement, and that the mean values of these measures were recorded.

One of the study limitations that deserves to be emphasized is the fact that the measurements were performed before the consultations in the waiting rooms of the clinics and, consequently, less subject to the white coat effect.[26] However, this fact did not generate significant differences between the BP measured by the researchers when compared to that measured by the physicians responsible for the care.

Another potential limitation is the fact that the study was carried out in a school-hospital setting.

Such institutions, in which most of the consultations are carried out with an academic purpose by professionals directly involved in medical education would, in theory, offer a better-quality service.[27,28] Thus, the chance of not following the recommendation to measure BP would be lower than in other service environments. This rationale increases the concern regarding the data obtained in this study, as they may be underestimated in relation to outpatient care in general, outside the academic environment.

The data of this study clearly show that the recommendation to measure the patients' BP at all medical evaluations, regardless of the medical specialty, is not being followed. Moreover, they suggest that the recommendation to measure BP at least three times and use the mean of the last two measures as the BP value is a desirable approach. Measures to raise the awareness of the medical profession in this sense should be taken immediately and as comprehensively as possible. Perhaps, in doing so, we will be able to offer to all the patients, at the doctor's offices, a low-cost, easy-to-apply BP screening and monitoring tool.

Conclusions

Blood pressure was not measured in many medical consultations, especially in surgical outpatient clinics. There was no difference between the blood pressure values obtained after following the correct technique in relation to those recorded in patients' files.

Author contributions

Conception and design of the research: Maynarde IG, Jardim TSV, Jardim PCBV. Acquisition of data: Maynarde IG, Rocca AR, Lin LYC, Santos NMC, Serafim XLM. Analysis and interpretation of the data: Maynarde IG, Jardim TSV, Sousa ALL, Rocca AR, Lin LYC, Santos NMC, Serafim XLM, Jardim PCBV. Statistical analysis: Maynarde IG, Jardim TSV, Sousa ALL. Writing of the manuscript: Maynarde IG, Jardim TSV, Sousa ALL. Critical revision of the manuscript for intellectual content: Maynarde IG, Jardim TSV, Souza WKSB, Sousa ALL, Rocca AR, Lin LYC, Santos NMC, Sampaio DPS, Serafim XLM, Jardim PCBV.

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 Israel Guilharde Maynarde's internal medicine residency graduation work at Hospital das Clínicas da Universidade Federal de Goiás.

References

1. Sociedade Brasileira de Cardiologia. Sociedade Brasileira de Hipertensão. Sociedade Brasileira de Nefrologia. VI Diretrizes Brasileiras de Hipertensão.*Arq Bras Cardiol.2010;* 95(1supl1):1-51.
2. Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension. Blood Pressure.2013;22(4):193-278.
3. National Institute for Health and Clinical Care Excellence: Guidance Clinical Guidelines. London: National Institute for Health and Care Excellence (UK);2003.
4. Leung AA, Nerenberg K, Daskalopoulou SS, BBrien n K, Zammke KB, m Dasgupta K, et al. Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, Assessment of Risk, Prevention, and Treatment of Hypertension. Can J Cardiol. 2016;32(5):569-88.
5. A'Court C, Stevens R, Sanders S, Ward A, McManus R, Heneghan C. Type and accuracy of sphygmomanometers in primary care: a cross-sectional observational study. Br J Gen Pract. 2011;61(590):e598-603.
6. Rouse A, Marshall T. The extent and implications of sphygmomanometer calibration error in primary care. J *Hum Hypertens.* 2001;15(9):587-591.
7. Coleman AJ, Steel SD, Ashworth M, Vowler SL, Shennan A. Accuracy of the pressure scale of sphygmomanometers in clinical use within primary care. *Blood Press Monit.* 2005;10(4):181-8.
8. Felix-Redondo FJ, Fernandez-Berges D, Espinosa-Garcia J, Pozuelos-Estrada J, Molina-Martinez LM, Perez-Castan JF, et al. Level of blood pressure control in a hypertensive population when measurements are performed outside the clinical setting. *Cardiol J.* 2009;16(1):57-67.
9. Segre CA, Ueno RK, Warde KRJ, Accorsi TA, Miname MH, Chi CK, et al. White-coat hypertension and normotension in the League of Hypertension of the Hospital das Clínicas, FMUSP: prevalence, clinical and demographic characteristics. *Arq Bras Cardiol.* 2003;80(2):122-6.
10. Myers MG, Oh PI, Reeves RA, Joyner CD. Prevalence of white coat effect in treated hypertensive patients in the community. *Am J Hypertens.* 1995;8(6):591-597.
11. Broad J, Wells S, Marshall R, Jackson R. Zero end-digit preference in recorded blood pressure and its impact on classification of patients for pharmacologic management in primary care - PREDICT-CVD-6. *The British journal of general practice : the journal of the Royal College of General Practitioners.* 2007;57(544):897-903.
12. Tolonen H, Koponen P, Naska A, Mannisto S, Broda G, Palossari T, et al. Challenges in standardization of blood pressure measurement at the population level. *BMC Med Res Methodol.* 2015 Apr 10, 15:33.
13. Alavarce DC, Pierin AMG, Mion Jr D. A pressão arterial está sendo medida? *Ver Esc Enferm USP.* 2000;34:84-90.

14. Ozone S, Shaku F, Sato M, Takayashiki A, Tsutsumi M, Maeno T. Comparison of blood pressure measurements on the bare arm, over a sleeve and over a rolled-up sleeve in the elderly. *Fam Pract.* 2016;33(5):517-22.

15. van Popele NM, Bos WJ, de Beer NA, van Der Kuip DA, Hoffman A, Grobboce DF, et al. Arterial stiffness as underlying mechanism of disagreement between an oscillometric blood pressure monitor and a sphygmomanometer. *Hypertension.* 2000;36(4):484-8.

16. Zheng D, Giovannini R, Murray A. Effect of respiration, talking and small body movements on blood pressure measurement. *J Hum Hypertens.* 2012;26(7):458-462.

17. Pierin AM, Alavarce DC, Gusmao JL, Halpern A, Mion DJr. Blood pressure measurement in obese patients: comparison between upper arm and forearm measurements. *Blood Press Monit.* 2004;9(3):101-5.

18. Levy J, Gerber LM, Wu X, Mann SJ. Nonadherence to Recommended Guidelines for Blood Pressure Measurement. J Clin Hypertens. (Greenwich). 2016;18(11):1157-61.

19. Ringrose JS, McLean D, Ao P, Yousefi F, Sankaralingam S, Milay J, et al.Effect of cuff design on auscultatory and oscillometric blood pressure measurements. *Am J Hypertens.* 2016;29(9):1063-9.

20. Mbanya VN, Mbanya J-C, Kufe C, Kengne AP. Effects of single and multiple blood pressure measurement Ssrategies on the prediction of prevalent screen-detected Diabetes Mellitus: A Population-Based Survey. J Clin Hypertens. 2016;18(9):864-70.

21. Mion Junior D, Silva GVd, Gusmão JLd, et al. Os médicos brasileiros seguem as diretrizes brasileiras de hipertensão? *Arq Bras Cardiol.* 2007;88(2):212-7.

22. Mion Júnior D, Pierin AMG, Lessa I, Nobre F. Devices and Techniques for Blood Pressure Measurement and Criteria for Hypertension Adopted by Brazilian Physicians: Exploratory Study. *Arq Bras Cardiol.* 2002;79:(6)597-600.

23. Myers MG, Godwin M, Dawes M, Kiss A, Tobe SW, Kaczorowski J. Measurement of blood pressure in the office: recognizing the problem and proposing the solution. *Hypertension.* 2010;55(2):195-200.

24. Fagard RH, Van Den Broeke C, De Cort P. Prognostic significance of blood pressure measured in the office, at home and during ambulatory monitoring in older patients in general practice. *J Hum Hypertens.* 2005;19(10):801-7.

25. Myers MG. The great myth of office blood pressure measurement. *J Hypertens.* 2012;30(10):1894-8.

26. Cuspidi C, Rescaldani M, Tadic M, Sala C, Grassi G, Mancia G. White-coat hypertension, as defined by ambulatory blood pressure monitoring, and subclinical cardiac organ damage: a meta-analysis. *J Hypertens.* 2015;33(1):24-32.

27. Campos GWdS. Educação médica, hospitais universitários e o Sistema Único de Saúde. *Cad Saúde Pública.Rio de Janeiro.* 1999;15(1):187-94.

28. Machado SP, Kuchenbecker R. Desafios e perspectivas futuras dos hospitais universitários no Brasil. *Cienc saude coletiva [[online].2007;12(4):871-7.*

International Journal of Cardiovascular Sciences. 2017;30(4):299-306

ORIGINAL ARTICLE

12-Month Clinical Follow-Up of Patients Undergoing Early Invasive Strategy by the Transradial or Transfemoral Approach with Vascular Closure Device

Pedro Beraldo de Andrade,[1] Luiz Alberto Piva e Mattos,[2] Fabio Salerno Rinaldi,[1] Igor Ribeiro de Castro Bienert,[3] Robson Alves Barbosa,[1] Sérgio Kreimer,[2] Vinícius Cardoso Esteves,[2] Marden André Tebet,[2] André Labrunie,[4] Amanda Guerra de Moraes Rego Sousa[5]

Santa Casa de Marília, Marília, SP;[1] Rede Dor São Luiz, Rio de Janeiro, RJ;[2] Hospital das Clínicas da Faculdade de Medicina de Marília (FAMEMA), Marília, SP;[3] Hospital do Coração de Londrina, Londrina, PR;[4] Instituto Dante Pazzanese de Cardiologia, São Paulo, SP[5] – Brazil

Abstract

Background: The radial approach reduces the prevalence of vascular complications, major bleeding and mortality when compared to the femoral approach. However, the last still prevails as the preferred approach for the performance of invasive coronary procedures, requiring the adoption of strategies to minimize complications.

Objectives: To compare the survival free of major adverse cardiovascular events at 12 months in patients undergoing early intervention strategy by the radial or femoral access with vascular closure device.

Methods: Randomized non inferiority trial involving 240 non-ST-segment elevation acute coronary syndrome patients. The survival free of death, myocardial infarction or stroke was estimated by the Kaplan-Meier method and compared using the log rank test.

Results: The 30-day rate of vascular complications in the arterial puncture site was 12.5% in the Angio-Seal group and 13.3% in the radial group (p = 1.000). The 12-month incidence of major bleeding or blood transfusion did not differ between groups (2.5% vs. 1.7%, p = 1.000). There was no difference in survival free of major adverse cardiovascular events (90.8% versus 94.2%, p = 0.328).

Conclusions: There was no distinction between the techniques in survival free of major adverse cardiovascular events at 12 months of follow-up. Clinical trials with greater statistical power are needed to validate these findings. (Int J Cardiovasc Sci. 2017;30(4):299-306)

ClinicalTrials.gov Identifier: NCT01653587

Keywords: Myocardial Ischemia; Percutaneous Coronary Percutaneous; Radial Artery; Hemostasis.

Introduction

The early interventionist strategy represents an important step in the treatment of non-ST segment elevation myocardial infarction (NSTEMI), due to its superiority in reducing death and reinfarction when compared to the conservative strategy.[1] Since the completion of invasive coronary procedures undergoing therapy Intense antithrombotic therapy predisposes to the occurrence of severe bleeding, with a potential prognostic impact, strategies aimed at preventing this complication guide the contemporary management of this patient profile.[2]

In this context, the option for radial access, in detriment to the femoral one, has been shown to reduce mortality and severe bleeding rates, especially after obtaining proficiency with the technique.[3] In turn, the efficacy and safety resulting from the adoption of vascular occlusion devices (VOD) in the prevention of complications in procedures carried out through the

Mailing Address: Pedro Beraldo de Andrade
Serviço de Hemodinâmica e Cardiologia Intervencionista da Santa Casa de Marília – Avenida Vicente Ferreira, 828. Postal Code: 17515-900, Marília, São Paulo – Brazil
E-mail: pedroberaldo@gmail.com

DOI: 10.5935/2359-4802.20170057

Manuscript received August 15, 2016, revised manuscript March 02, 2017, accepted March 08, 2017.

lower limb is still a matter of debate.[4] In the randomized clinical trial *Angio-Seal* versus the *Radial approach in acute coronary syndrome* (ARISE) the systematic use of a VOD in patients undergoing invasive stratification by femoral access was shown to be not inferior to radial access with respect of the incidence of vascular complications related to the arterial puncture site at 30 days.[5]

The objective of the present pre-specified analysis of the ARISE study was to compare the incidence of serious adverse cardiovascular events in clinical follow-up of 12 months, according to the access route adopted.

Methods

The design and rationale of the ARISE pilot study has been previously published.[6] In summary, from July 2012 to March 2015, 240 patients with a diagnosis of NSTEMI who underwent invasive stratification were randomized to perform the procedure by radial access or femoral vein with VOD Angio-Seal (St. Jude Medical, St. Paul, Minnesota, US). The choice of Angio-Seal relied on the ease of handling, lower cost and greater casuistry published in the literature in its favor. Patients should present at least two of three markers of greatest clinical severity: ischemic changing in 12-lead electrocardiogram, positivity of biomarkers of myocardial necrosis or more than 60 years age. The objective of this analysis was to compare the techniques for free survival of serious adverse cardiovascular events at 12 months, defined as general mortality, acute myocardial infarction (AMI) or cerebrovascular accident (CVA).

Study procedures

For the randomization process an aleatory sequence was obtained through computational algorithms and maintained in individual envelopes, allowing allocation concealment. The coronarography, by both, radial and femoral accesses, was performed using the Judkins technique, using arterial introducers with 6 French diameter. Percutaneous coronary intervention (PCI) was indicated when a lesion was determined as a culprit lesion of the clinical event, with a severity of stenosis diameter ≥ 70%, showing a high probability of angiographic success, being performed immediately after the end of coronary angiography and left ventriculography (ad hoc) . Anticoagulation in the hemodynamic laboratory was obtained with intravenous 85-100 U / kg unfractionated heparin, suited to prior subcutaneous administration of enoxaparin or fondaparinux. In order to obtain haemostasis in the radial technique, the TR BAND radial compression device (*Terumo Corporation*, Tokyo, Japan) was applied, according to a protocol previously validated by our center, aiming at maintenance of patent anterograde flow.[7] In the femoral technique, The VOD Angio-Seal, preceded by the systematic accomplishment of femoral angiography and maintaining absolute rest in the bed for 60 minutes after achieving adequate hemostasis. The success of the device was defined as the obtaining the adequate hemostasis at the end of the procedure, without the need to apply other compression methods.

Markers of myocardial necrosis, hemoglobin and hematocrit were measured pre-procedure and between 12 and 24 hours after its completion. Electrocardiogram was performed soon after the procedure or before the suspicion of a new ischemic event. Vascular complications related to arterial access were evaluated during hospitalization and on-site visit in 30 days after the procedure. The late assessment of the occurrence of cardiovascular events was obtained through telephone contact at six and twelve months, as well as by electronic chart review.

Statistical analysis

Absolute and relative frequencies were presented for the categorical and numerical variables, summary-measures (mean and standard deviation). The existence of associations between two categorical variables was verified using the chi-square test, or alternatively in cases of small samples, Fisher's exact test. The comparison of means between two groups was performed using Student's t-test for independent samples. The survival function free of serious adverse cardiovascular events (death, AMI or CVA) was estimated by the Kaplan-Meier model and compared using the log rank test (Mantel-Cox). A significance level of 5% was used for all statistical tests. Statistical analyzes were performed using the statistical software SPSS 20.0.

The study was approved by the local research ethics committee and a free and informed consent form was obtained from every participant. There was no source of external funding and the authors are entirely responsible for the design, conduction, data analysis and final drafting of the manuscript.

Results

Figure 1 illustrates the inclusion and randomization flowchart of the study. The mean age was 63 years, 30.8% were diabetic, troponin positive was detected in 84.2% of the sample and, except for the greater prevalence of women in the radial group, no differences were observed between the groups (Table 1). 65% of the evaluated sample was classified as low or very low risk for bleeding from the CRUSADE score. PCI was performed in 86.7% of the cases and the characteristics of the procedures are expressed in Table 2. Stents were implanted in 97.6% of the cases, with predominance of non-pharmacological stents due to public health system reimbursement policies.

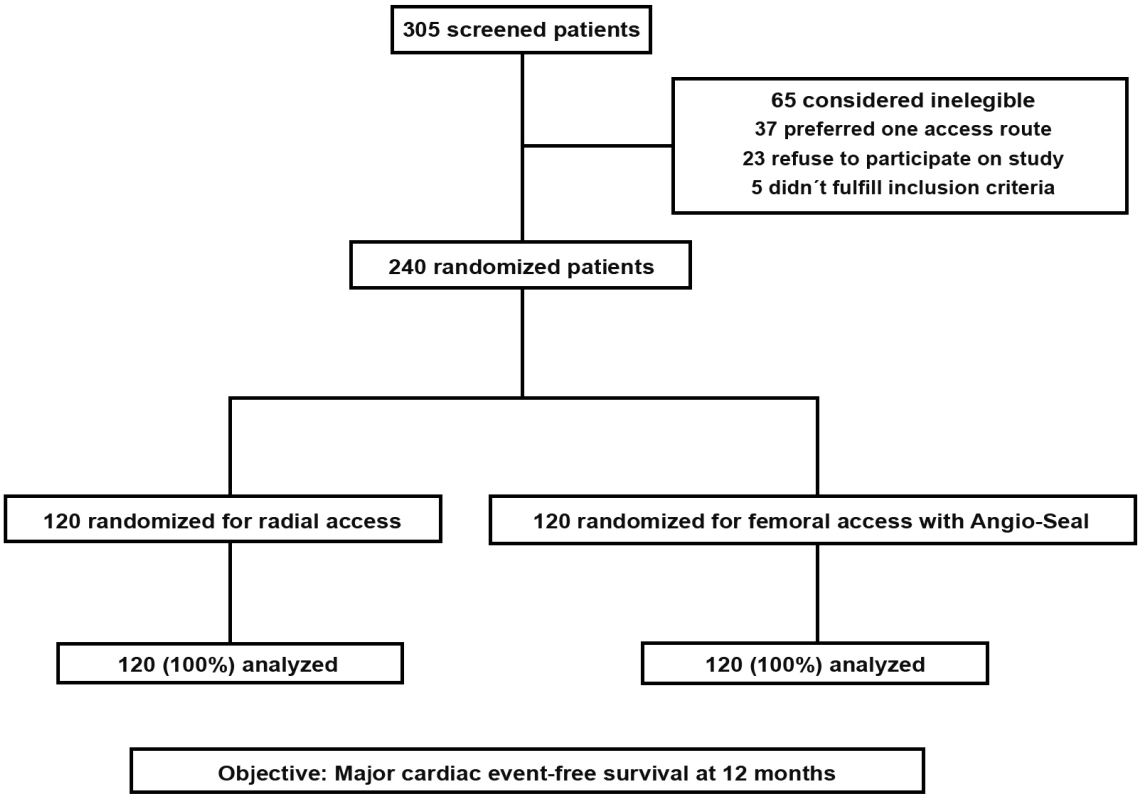

Figure 1 – *Inclusion and randomization flowchart of the ARISE study.*

Angiographic and procedural success rates were high (97.6% and 95.2%, respectively). Hemostasis with TR BAND was obtained in 100% of the procedures by radial access, with anterograde flow demonstrated by the oximetric curve in 102 patients (85%). In six (5%) patients in the femoral group, the Angio-Seal device was not sufficient to obtain hemostasis, requiring additional manual compression for a period longer than 10 minutes. The rate of vascular complications at the 30-day arterial puncture site was 12.5% in the Angio-Seal group, at the cost of hematomas > 5 cm, and 13.3% in the radial group, at hematomas > 5 cm (6.7%) and asymptomatic occlusion of the radial artery (5.8%), with no significant difference. There were no cases of arteriovenous fistula, retroperitoneal hematoma, compartment syndrome, limb ischemia, nerve damage or the need for repairing vascular surgery.

Table 1 – Clinical characteristics of patients

Variable	General (n=240)	Angio-Seal (n=120)	Radial (n=120)	p
Age, years (mean(standard deviation SD))	63.0 ± 10.7	63.6 ± 10.2	62.5 ± 11.2	0.438
Female gender, n (%)	64 (26.7%)	24 (20.0%)	40 (33.3%)	0.020
Diabetes mellitus, n (%)	74 (30.8%)	41 (34.2%)	33 (27.5%)	0.263
Hypertensionl, n (%)	179 (74.6%)	93 (77.5%)	86 (71.7%)	0.299
Dyslipidemia, n (%)	104 (43.3%)	52 (43.3%)	52 (43.3%)	1.000
Positive family history, n (%)	72 (30.0%)	35 (29.2%)	37 (30.8%)	0.778
Smoking, n (%)	82 (34.2%)	41 (34.2%)	41 (34.2%)	1.000
Previous myocardial infarction, n (%)	13 (5.4%)	5 (4.2%)	8 (6.7%)	0.392
Previous coronary angioplasty, n (%)	11 (4.6%)	4 (3.3%)	7 (5.8%)	0.354
Previous revascularization surgery, n (%)	2 (0.8%)	1 (0.8%)	1 (0.8%)	1.000
Previous stroke, n (%)	16 (6.7%)	11 (9.2%)	5 (4.2%)	0.121
Creatinine clearance < 60 mL/min, n (%)	50 (20.8%)	20 (16.7%)	30 (25.0%)	0.112
Peripheral arterial disease, n (%)	8 (3.3%)	5 (4.2%)	3 (2.5%)	0.472
GRACE score ≥ 140, n (%)	119 (49.6%)	58 (48.3%)	61 (50.8%)	0.699

The ischemic endpoints after 1 year according to the used access via are expressed on Table 3. The rate of severe bleeding or blood transfusion was 2.5% in the Angio-Seal group and 1.7% in the radial group (p = 1,000). Figure 2 illustrates the free survival curve of serious adverse cardiovascular events compound at 12 months, with no distinction being made between techniques (90.8% versus 94.2%, p = 0.328).

Discussion

The approach of NSTEMI contemplates invasive risk stratification risk and potent antithrombotic pharmacotherapy, a strategy that promotes the reduction of ischemic adverse events at the expense of increased bleeding risk. In this scenario, the adoption of the radial technique as an alternative to the femoral technique was shown to be superior in the reduction of vascular complications related to the arterial puncture site and consequently of clinical outcomes.[8] Encouraging results from unicentric studies with modest sampling were corroborated by large randomized meta-analyzes. Reviewing the data from patients with acute coronary syndrome conducted in a meta-analysis of 17 studies and 19,328 procedures, radial access promoted a significant reduction of 27% in mortality and 40% in severe bleeding.[9] Including all spectra of the atherosclerotic coronary disease, meta-analysis with 22,843 participants maintained the observed benefit with reduction of 29% in total mortality and 47% reduction in severe bleeding.[10]

However, femoral access still prevails as a preferential route for the accomplishment of invasive coronary procedures. In Brazil, it is estimated that the use of the radial technique in PCI make up currently about 30% of the cases.[11,12] Thus, it is imperative to adopt measures able to provide greater safety to the procedure, such as reducing the diameter of the devices endovascular, early removal of the arterial introducer, fluoroscopy or ultrasound guided femoral puncture. On the other hand, the use of DOV in obtaining haemostasis by the femoral technique shows conflicting data about its efficacy, supported mainly by negative studies involving first generation devices, many of which are no longer commercialized.[13,14] However, contemporary analyzes indicate superiority Strategy against manual compression. Among 85,048 ICPs performed between 2007 and 2009, registered in a multicenter registry in the state of Michigan, of which 28,528 used a DOV, they promoted a significant reduction of vascular

Table 2 – Angiographic characteristics and procedures

Variable	General (n=240)	Angio-Seal (n=120)	Radial (n=120)	P
Ad hoc angioplasty, n (%)	208 (86.7%)	107 (89.2%)	101 (84.2%)	0.255
Volume of contrast, ml (mean(standard deviation SD))	163.6 ± 46.9	168.1 ± 47.8	159.1 ± 45.7	0.140
Fluoroscopy time, min (mean(standard deviation SD))	8.5 ± 5.5	8.6 ± 6.0	8.5 ± 4.9	0.879
Enoxaparin, n (%)	114 (47.5%)	53 (44.2%)	61 (50.8%)	0.301
Fondaparinux, n (%)	117 (48.7%)	63 (52.5%)	54 (45.0%)	0.245
Glycoprothein Inhibitor, n (%)	17 (7.1%)	7 (5.8%)	10 (8.3%)	0.450
AAS, n (%)	240 (100%)	120 (100%)	120 (100%)	–
Clopidogrel, n (%)	195 (81.2%)	99 (82.5%)	96 (80.0%)	0.620
Ticagrelor, n (%)	45 (18.7%)	21 (17.5%)	24 (20.0%)	0.620
Treatment time, days (mean(standard deviation SD))	3.7 ± 2.5	3.9 ± 2.7	3.6 ± 2.3	0.413
Atherosclerotic Disease, n (%)				0.316
No lesion	26 (10.8%)	9 (7.5%)	17 (14.2%)	
Uniarterial	112 (46.7%)	57 (47.5%)	55 (45.8%)	
Biarterial	70 (29.2%)	39 (32.5%)	31 (25.8%)	
Triarterial	32 (13.3%)	15 (12.5%)	17 (14.2%)	
Ejection fraction, n (%)				0.433
Normal	157 (65.4%)	79 (65.8%)	78 (65.0%)	
Discrete disfunction	42 (17.5%)	17 (14.2%)	25 (20.8%)	
Moderate disfunction	26 (18.8%)	15 (12.5%)	11 (9.2%)	
Severe disfunction	15 (6.2%)	9 (7.5%)	6 (5.0%)	
Culprit artery, n (%)				0.562
Left coronary artery trunk	2 (0.9%)	2 (1.8%)	0 (0.0%)	
Anterior descending	106 (50.2%)	53 (48.6%)	53 (52.0%)	
Circumflex	36 (17.1%)	17 (15.6%)	19 (18.6%)	
Right coronary	65 (30.8%)	36 (33.0%)	29 (28.4%)	
Ramus intermedius	2 (1.0%)	1 (1.0%)	1 (1.0%)	
Stent, n (%)	203 (97.6%)	105 (98.1%)	98 (97.0%)	0.676
Ballon, n (%)	5 (2.1%)	2 (1.7%)	3 (2.5%)	1.000
Number of stents, (mean(standard deviation SD))	1.1 ± 0.4	1.2 ± 0.4	1.1 ± 0.4	0.406
Number of lesions, (mean(standard deviation SD))	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	0.629
Stent diameter, (mean(standard deviation SD))	3.1 ± 0.6	3.1 ± 0.6	3.1 ± 0.6	0.724
Extension of stent, (mean(standard deviation SD))	23.4 ± 7.5	23.4 ± 7.8	23.4 ± 7.3	0.948
Non-drug-eluting stent n (%)	200 (98.5%)	103 (98.1%)	97 (99.0%)	1.000
Drug-eluting stent, n (%)	3 (1.5%)	2 (1.9%)	1 (1.0%)	1.000
Crossover techniques, n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	–
Angiographic success, n (%)	203 (97.6%)	105 (98.1%)	98 (97.0%)	0.676
Procedure Success, n (%)	198 (95.2%)	102 (95.3%)	96 (95.0%)	1.000
Device success, n (%)	234 (97.5%)	114 (95.0%)	120 (100.0%)	0.029
Time to discharge, days (mean(standard deviation SD))	1,4 ± 1.4	1.5 ± 1.8	1.3 ± 0.8	0.311

Table 3 – Ischemic adverse cardiovascular events in 12 months

Variable	General (n=240)	Angio-Seal (n=120)	Radial (n=120)	p
Cardiovascular death, n (%)	10 (4.2%)	6 (5.0%)	4 (3.3%)	0.769
Death, n (%)	12 (5.0%)	7 (5.8%)	5 (4.2%)	0.749
Acute myocardial infarction, n (%)	6 (2.5%)	1 (0.8%)	5 (4.2%)	0.213
Stent thrombosis, n (%)	4 (1.7%)	1 (0.8%)	3 (2.5%)	0.622
Stroke, n (%)	1 (0.4%)	1 (0.8%)	0 (0.0%)	1.000
Major adverse cardiac events, n (%)	18 (7.5%)	11 (9.2%)	7 (5.8%)	0.463

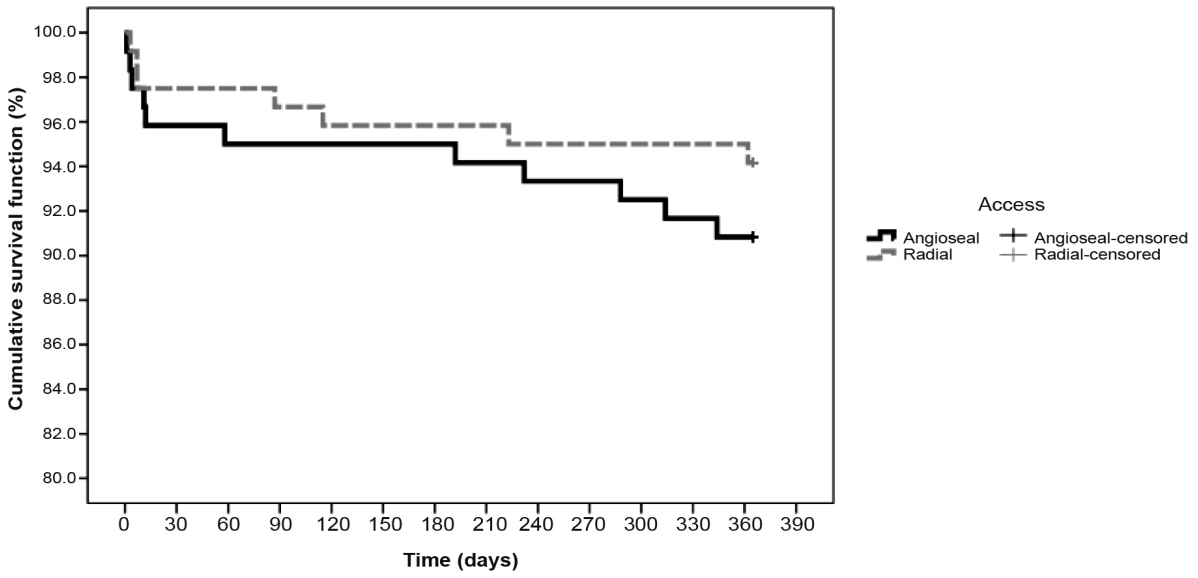

Figure 2 – *Probability of death, acute myocardial infarction or stroke-free survival at 12 months according to the access route adopted.*

complications and the need for transfusion.[15] The British national real-world registry encompassing 271,485 therapeutic procedures performed between 2006 to 2011 showed a lower 30-day DOV-favorable mortality rate, especially among women, acute coronary syndrome as a form of clinical presentation and recent thrombolysis.[16]

The main question still open is whether the DOV present the same effectiveness of the radial technique in the reduction of vascular complications and bleeds related to the access route. The ARISE study adds data to this questioning, since it is the first randomized clinical trial comparing the two strategies in a population of patients with SIMISSST. No differences were observed between the techniques regarding the incidence of vascular complications at 30 days and serious adverse cardiovascular events at 12 months. In fact, it is postulated that the benefits derived from the radial technique are mainly due to the reduction in the prevalence of severe bleeding and the need for blood transfusion,[17] which was not observed in our study. Our findings differ from the few publications comparing the radial access to VOD, where the first is associated with a significant reduction of vascular complications, as the main difference

between these cases and our study being the non-random nature of them.[18,19]

The study has limitations, the main one being its small sample size and statistical nature of hypothesis generating. In addition, in all procedures performed by femoral access, the diameter of the devices used was 6 French, and it was not possible to extend the findings to cases where larger diameter devices were used. Since the study population covered predominantly low-risk bleeding patients, the results can not be expanded to situations characterized by a higher risk of bleeding, especially for patients with ST-segment elevation myocardial infarction who underwent primary PCI. The Angio-Seal cost-effectiveness analysis, although attested in previous publications,[20,21] was not the scope of this analysis and requires the evaluation of different variables, such as work process in the interventional cardiology laboratory, nature of the procedure, patient risk profile and reimbursement policies.

Conclusions

In patients submitted to the early interventional strategy in the ARISE pilot study, randomized to the radial or femoral technique with a vascular occlusion device, no distinction was observed in survival free of serious adverse cardiovascular events at 12 months of follow-up. Clinical trials with greater statistical power are necessary for the validation of these findings.

Author contributions

Conception and design of the research: Andrade PB, Mattos LAP, Labrunie A, Sousa AGMR. Acquisition of data: Andrade PB, Rinaldi FS, Bienert IRC, Barbosa RA, Labrunie A. Analysis and interpretation of the data: Andrade PB. Statistical analysis: Andrade PB. Obtaining financing: Andrade PB. Writing of the manuscript: Andrade PB. Critical revision of the manuscript for intellectual content: Andrade PB, Mattos LAP, Kreimer S, Esteves VC, Tebet MA, Labrunie A, Sousa AGMR.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

This article is part of the thesis of Doctoral submitted by Pedro Beraldo de Andrade, from Universidade de São Paulo.

References

1. Nicolau JC, Timerman A, Marin-Neto JA, Piegas LS, Barbosa CJ, Franci A, et al; Sociedade Brasileira de Cardiologia. [Guidelines of Sociedade Brasileira de Cardiologia for unstable angina and non-ST-segment elevation myocardial infarction (II edition, 2007) 2013-2014 update]. Arq Bras Cardiol. 2014;102(3 Suppl 1):1-61.
2. Vora AN, Peterson ED, McCoy LA, Garratt KN, Kutcher MA, Marso SP, et al. The impact of bleeding avoidance strategies on hospital-level variation in bleeding rates following percutaneous coronary intervention: insights from the National Cardiovascular Data Registry CathPCI Registry. JACC Cardiovasc Interv. 2016;9(8):771-9.
3. Andò G, Capodanno D. Radial versus femoral access in invasively managed patients with acute coronary syndrome: a systematic review and meta-analysis. Ann Intern Med. 2015;163(12):932-40.
4. Patel MR, Jneid H, Derdeyn CP, Klein LW, Levine GN, Lookstein RA, et al; American Heart Association Diagnostic and Interventional Cardiac Catheterization Committee of the Council on Clinical Cardiology, Council on Cardiovascular Radiology and Intervention, Council on Peripheral Vascular Disease, Council on Cardiovascular Surgery and Anesthesia, and Stroke Council. Arteriotomy closure devices for cardiovascular procedures: a scientific statement from the American Heart Association. Circulation. 2010;122(18):1882-93. Erratum in: Circulation. 2010;122(18):e507.
5. Andrade PB, Mattos LA, Rinaldi FS, Bienert IC, Barbosa RA, Nogueira EF, et al. Comparison of a vascular closure device versus the radial approach to reduce access site complications in non-ST-segment elevation acute coronary syndrome patients: the Angio-Seal versus the Radial approach In acute coronary Syndrome (ARISE) trial. Catheter Cardiovasc Interv. 2016 Aug 12.[Epub ahead of print].
6. de Andrade PB, E Mattos LA, Tebet MA, Rinaldi FS, Esteves VC, Nogueira EF, et al. Design and rationale of the Angio Seal versus the Radial approach In acute coronary SyndromE (ARISE) trial: a randomized comparison of a vascular closure device versus the radial approach to prevent vascular access site complications in non-ST-segment elevation acute coronary syndrome patients. Trials. 2013;14:435.
7. Andrade MV, Andrade PB, Barbosa RA, Tebet MA, Silva FS, Labrunie A, et al. Validation of a protocol to achieve hemostasis using the TR BandTM radial compression device after percutaneous coronary intervention. Rev Bras Cardiol Invasiva.2011;19(2):184-8.
8. Jolly SS, Yusuf S, Cairns J, Niemelä K, Xavier D, Widimsky P, et al; RIVAL trial group. Radial versus femoral access for coronary angiography and intervention in patients with acute coronary syndromes (RIVAL): a randomized, parallel group, multicentre trial. Lancet. 2011;377(9775):1409-20. Erratum in: Lancet. 2011;377(9775):1408. Lancet. 2011;378(9785):30.

9. Andò G, Capodanno D. Radial access reduces mortality in patients with acute coronary syndromes: results from an updated trial sequential analysis of randomized trials. JACC Cardiovasc Interv. 2016;9(7):660-70.

10. Ferrante J, Rao SV, Jüni P, Da Costa B, Reimers B, Condorelli G, et al. Radial versus femoral access for coronary interventions across the entire spectrum of patients with coronary artery disease: a meta-analysis of randomized trials. JACC Cardiovasc Interv. 2016;9(14):1419-34.

11. Andrade PB, Tebet MA, Andrade MV, Labrunie A, Mattos LA. Radial approach in percutaneous coronary interventions: current status in Brazil. Arq Bras Cardiol. 2011;96(4):312-6.

12. Rinaldi FS, Andrade PB, Andrade MV, Mattos LA, Santucci EV, Cavalcante MA, et al. In-hospital and Six-Month Antithrombotic Therapy after Primary Percutaneous Coronary Intervention: Analysis of Acute Coronary Care Evaluation of Practice (ACCEPT) Registry. Rev Bras Cardiol Invasiva. 2013;21(1):30-5.

13. Koreny M, Riedmuller E, Nikfardjam M, Siostrzonek P, Mullner M. Arterial puncture closing devices compared with standard manual compression after cardiac catheterization: systematic review and meta-analysis. JAMA. 2004;291(3):350-7.

14. Nikolsky E, Mehran R, Halkin A, Aymong ED, Mintz GS, Lasic Z, et al. Vascular complications associated with arteriotomy closure devices in patients undergoing percutaneous coronary procedures: a meta-analysis. J Am Coll Cardiol. 2004;44(6):1200-9.

15. Gurm HS, Hosman C, Share D, Moscucci M, Hansen BB; Blue Cross Blue Shield of Michigan Cardiovascular Consortium. Comparative safety of vascular closure devices and manual closure among patients having percutaneous coronary intervention. Ann Intern Med. 2013;159(10):660-6.

16. Farooq V, Goedhart D, Ludman P, de Belder MA, Harcombe A, et al; British Cardiovascular Intervention Society and the National Institute for Cardiovascular Outcomes Research. Relationship between femoral vascular closure devices and short-term mortality from 271845 percutaneous coronary intervention procedures performed in the United Kingdom between 2006 and 2011: a propensity score-corrected analysis from the British Cardiovascular Intervention Society. Circ Cardiovasc Interv. 2016;9(6):e003560.

17. Huff CM, Kapadia S, Rao SV. Mechanisms by which transradial approach may reduce mortality in ST-segment-elevation myocardial infarction. Circ Cardiovasc Interv. 2014;7(4):621-7.

18. Sciahbasi A, Fischetti D, Picciolo A, Patrizi R, Sperduti I, Colonna G, et al. Transradial access compared with femoral puncture closure devices in percutaneous coronary procedures. Int J Cardiol. 2009;137(3):199-205.

19. Mann T, Cowper PA, Peterson ED, Cubeddu G, Bowen J, Giron L, et al. Transradial coronary stenting: comparison with femoral access closed with an arterial suture device. Catheter Cardiovasc Interv. 2000;49(2):150-6.

20. Kerré S, Kustermans L, Vandendriessche T, Bosmans J, Haine SE, Miljoen H, et al. Cost-effectiveness of contemporary vascular closure devices for the prevention of vascular complications after percutaneous coronary interventions in an all-comers PCI population. EuroIntervention. 2014;10(2):191-7.

21. Resnic FS, Arora N, Matheny M, Reynolds MR. A cost-minimization analysis of the Angio-Seal vascular closure device following percutaneous coronary intervention. Am J Cardiol. 2007;99(6):766-70.

International Journal of Cardiovascular Sciences. 2017;30(4):307-312

ORIGINAL ARTICLE

Probabilistic Model for Prediction of Prognostics in Myocardial Revascularization: Complications in Coronary Surgery

Valcellos José da Cruz Viana,[1,2] Felipe Coelho Argolo,[3] Nilzo Augusto Mendes Ribeiro,[2] Augusto Ferreira da Silva Junior,[2] Luis Claudio Lemos Correia[1]

Escola Bahiana de Medicina e Saúde Pública,[1] Hospital Santa Izabel da Santa Casa de Misericórdia da Bahia,[2] Hospital Universitário Professor Edgard Santos,[3] Salvador, BA - Brazil

Abstract

Introduction: Risk scores evaluate pre-operatory risk and present support for clinical decisions, however the performance of these tools in samples different from the original ones remains unclear.

Objectives: Investigate the external validity of risk scores (STS and Euroscore) in cardiac surgery and the predictive performance of clinical features derived from the sample.

Methods: Retrospective Cohort study conducted between October, 2010, and April, 2015. We used logistic regression to identify risk factors for hospital morbidity. The sample was divided for cross-validation, with 2/3 of the patients selected for model fitting and 1/3 for prediction testing. The performance of risk scores and clinical features was evaluated through AUROC and calibraton the Hosmer-Lemeshow test (H-L).

Results: Data was retrieved from 472 patients who underwent coronary cardiac surgery in Hospital Santa Izabel da Santa Casa, BA. Mean age was 62.8 years old and 32.5% of the sample were women. Traditional surgical risk scores did not present significant discriminative performance for this sample. Factors associated with the outcome after adjusting for covariates were: age, previous myocardial revascularization and pre-surgical creatinine levels. The adjusted model presented similar discrimination and calibration values during training (AUROC = 0,72; IC 95% 0,59-0,84; H-L valor p: 0,41) and validation (AUROC = 0,70; IC 95% 0,55 - 0,84; H-L valor p: 0,197).

Conclusion: Traditional scores may be inaccurate when applied to different environments. New risk scores with good predictive power can be developed using local clinical variables. (Int J Cardiovasc Sci. 2017;30(4):307-312)

Keywords: Thoracic Surgery/complications; Myocardial Infarction; Myocardial Revascularization; Risk Factors; Forecasting.

Introduction

Multivariate probabilistic models have been used in cardiac surgery to estimate the risk of fatal and nonfatal complications.[1] The goal is to evaluate the balance between risks and benefits of procedures for patients, with a better allocation of resources.[2] There are some risk scores of death and occurrence of complications in patients undergoing myocardial revascularization surgery such as EuroSCORE[3] and STS Score.[4] Assessing the prognosis related to the natural history of a clinical condition, predictive variables are reproducible in different settings.[5,6] On the other hand, when predicting the success or complications of medical procedures, it is possible that predictor variables have a variable value depending on the environment in which the procedure is implemented. This is because differences in the way a treatment is applied can make patients more or less vulnerable to risk determinants. Using a retrospective cohort performed at a tertiary hospital in Salvador, the present study aimed to test the external validity of traditional risk scores for surgical myocardial revascularization, to identify risk markers for

Mailing Address: Felipe Coelho Argolo
Rua Oito de Dezembro, 190. Postal Code: 40150-000, Graça, Salvador, BA – Brazil
E-mail: felipe.c.argolo@hotmail.com, felipe.c.argolo@h1estatistica.com.br

DOI: 10.5935/2359-4802.20170049

Manuscript received September14, 2016; revised manuscript October 11, 2016; accepted March 03, 2017.

myocardial revascularization surgery, and to construct a regional prediction model for complications related to the procedure.

Methods

Study design

Observational study of a retrospective cohort, using a database retrieved from the institution's records, fed with variables recorded between preoperative and patient discharge, used for research, after approval by the hospital's ethics council, under the registry number 24304713.9.3001.5544.

Sample selection criteria

All patients submitted to myocardial revascularization surgery at our service at Santa Izabel Hospital between October 2010 and April 2015 were included in the study sample. Patients with associated surgeries or those performed at other institutions were excluded.

Variables studied

The variables included in the analysis were: Gender, age, weight, height, body mass index, chronic obstructive pulmonary disease (COPD) – use of bronchodilator or corticoid, peripheral arteriopathy – intermittent claudication, carotid artery obstruction greater than 50%; left ventricular dysfunction – moderate 30-50% and significant less than 30%; previous neurological dysfunction – motor dysfunction affecting ambulation or daily function; previous cardiac surgery – previous opening of the pericardium; pre-and postoperative serum creatinine; endocarditis – antibiotic therapy for endocarditis at the time of surgery; unstable angina – use of venous nitrate; recent infarction – less than 90 days; pulmonary hypertension – pulmonary artery systolic pressure greater than 60 mmHg; previous myocardial revascularization; post-infarction ventricular septal defect; diabetes – use of oral hypoglycemic or insulin; smoking; hypertension – antihypertensive use; dyslipidemia – total cholesterol greater than 200 mg / dl, hypertriglyceridemia greater than 150 mg / dl, HDL cholesterol less than 40 mg / dl women and less than 50 mg / dl men; number of coronary lesions greater than 75%; left coronary trunk lesion greater than 50%; preoperative hypoxemia – artery oxygen pressure lower than 60 mmHg, emergency / urgency surgery – need for intervention within 48 hours due to imminent risk of death or unstable clinical-hemodynamic status; hemodynamic instability – ventricular tachycardia, ventricular fibrillation, cardiac arrest, mechanical ventilation, intra-aortic balloon use.

Definition of outcome

The main analysis was performed considering the composite outcome of major morbidity, including: stroke, stroke (central neurological deficit persisting for more than 72 hours); Prolonged intubation (more than 48 hours); Reoperation (tamponade or hemostasis); Mediastinitis (need for surgical reintervention, plus antibiotic therapy with or without positive culture), and death within 30 days after the surgical procedure. The events that made up the outcome were chosen based on models developed and validated from previous studies in cardiovascular surgery.[7]

Statistical analysis

Three logistic regression models were adjusted to test the predictive power of the scores in the sample: *EuroSCORE, STS Mortality, and STS Morbidity*. Each model was adjusted using the points of the respective score as the only independent variable. A proper model was adjusted following the algorithm proposed by Hosmer and Lemeshow[8] considering results of bivariate analysis and biological plausibility. The sample was divided into two parts: cohort derivation, intended for bivariate analysis and fit of the models (2/3 of the original sample, randomly selected); Cohort validation to test the obtained model (1/3 of the original sample, randomly selected). After obtaining the coefficients from the sample used for derivation, the model was tested using the validation sample. The Area under ROC Curve (AUROC) and model adequacy statistics are presented for comparison purposes. The analyzes were conducted using the programming language and R development environment.

Results

Between October 2010 and April 2015, information from 472 consecutive patients submitted to myocardial revascularization was included in the database. No patient was excluded because of lack of information. The mean age was 63 ± 8.6 years, 22.5% were women, 37% were diabetics, 32% were smokers, 18% had left ventricular dysfunction and 29% had left coronary artery

disease. The incidence of the composite outcome was 37 cases (7.8%), resulting in death 12 (2.5%), stroke 15 (3.2%), cardiac tamponade 4 (0.8%), reoperation for revision of hemostasis 9 (1.9%), mediastinitis 1 (0.2%) and prolonged intubation 21 (4.4%).

Prognostic value of traditional risk scores

The EuroSCORE did not show accuracy for prediction of surgical complications, with C-statistic of 0.507 (95% CI 0.415 - 0.599, p = 0.310). The same was observed with the STS score, with STS Morbidity C-statistic of 0.568 (95% CI 0.473-0.665, p = 0.160) and STS Mortality of 0.550 (95% CI 0.452-0.643, p = 0.860). – Figure 1.

Derivation of the proper model

The variables predictor candidates were selected in 2/3 random of the total sample through univariate analysis, considering statistical significance (p < 0.20). Table 1. Multiple logistic regression analysis according to Hosmer-Lemeshow algorithm: cerebrovascular disease, previous myocardial revascularization, previous creatinine, age and ejection fraction.

The independent predictors, related to outcome, identified in the final model according to their statistical significance were: previous myocardial revascularization (OR 8.519 95% CI 1.026-59.381 p = 0.029), previous creatinine (OR 2,217 95% CI 0.815-6.018 p = 0.095) and age (OR 1.081 95% CI 1.025-1.145 p = 0.006). Table 2. In the shunt sample (2/3 of the total sample) the ROC curve was 0.72 (95% CI 0.60-0.84, p < 0.001). The resulting logistics model followed the formula below:

$$P(y) = \frac{1}{1 + e^{(8.422 + 0.07 * Age + 2.14 * MI_{prev} + 0.07 * Cr_{prev})}}$$

AgePrevious

Validation was performed in 168 patients (1/3 of the total sample) randomly selected. The score was discriminated by the area under the ROC curve of 0.70 (95% CI: 0.55-0.84); P = 0.008. Calibration by the Hosmer-Lemeshow test (p = 0.197).

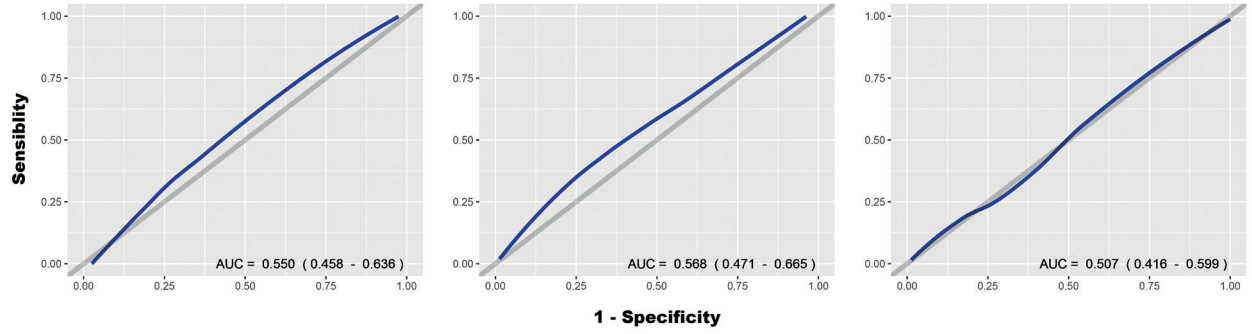

Figure 1 – *ROC Curves.*
A: STS Mortality; B: STS Morbidity; C: Euroscore.

Discussion

The use of multivariate models in the form of scores represents the most accurate mean to predict risk, being superior to that predicted subjectively by clinical impression.[9] And even showing good accuracy in different populations, especially in the clinical context,[5,6] the results of the present study suggest greater caution regarding the external validity of these scores in the field of cardiac surgery. In addition, a score developed in our local sample demonstrated good accuracy in an independent validation cohort, which may be the predictor in places with different characteristics of the traditional score validator centers. Models not readjusted to the local context may present bias in predicting risk in cardiac surgery and should be systematically compared with regional models.[10] Among the various scores used to predict death and occurrence of complications in cardiac surgery, EuroSCORE[3] and STSscore[4] are the most widespread

Table 1 – Bivariate analysis for combined outcome in derivation sub sample

	Total (n = 304)	Combined outcome		Value p
		No (n = 281)	Yes (n = 23)	
Age §	62.4 ± 8.9	61.9 ± 8.9	67.6 ± 8.2	0.003
Male gender	228 (75.0)	209 (74.4)	19 (82.6)	0.531
BMI(Kg/m²) * §	26.6 ± 3.6	26.6 ± 3.6	26.8 ± 3.9	0.788
Previous clearance //	83 (68 - 103)	84 (68 – 104)	81 (69 - 91)	0.454
Previous creatinine //	0,9 (0.8 - 1.1)	0.9 (0.8 - 1.1)	1.0 (0.9 - 1.3)	0.031
COPD †	6 (2.0)	6 (2.1)	0 (0.0)	1.000
Peripheral artery disease	13 (4.3)	11 (3.9)	2 (8.7)	0.619
Diabetes (In use of Hypoglycemic agent + Insulin)	109 (35.9)	100 (35.6)	9 (39.1)	0.909
Vascular Brain Disease	2 (0.7)	1 (0.4)	1 (4.3)	0.149
‡ Previous CABG	5 (1.6)	3 (1.1)	2 (8.7)	0.044
Emergency	19 (6.2)	18 (6.4)	1 (4.3)	1.000
Smoker	94 (30.9)	88 (31.3)	6 (26.1)	0.900
Antyhipertensive drug	263 (86.5)	242 (86.1)	21 (91.3)	0.728
Dyslipedemia	263 (86.5)	243 (86.5)	20 (87.0)	1.000
Coronary trunk lesion	87 (28.6)	82 (29.2)	5 (21.7)	0.597
Ejection Fraction				
> 50	238 (78.3)	221 (78.6)	17 (73.9)	
50-30	52 (17.1)	47 (16.7)	5 (21.7)	0.099
< 30	2 (0.7)	1 (0.4)	1 (4.3)	

** BMI: body mass index; † COPD: chronic obstructive coronary disease; ‡ MR: myocardial revascularization.*
All data presented with n (%), except stated otherwise. §Mean +- Standard deviation. // Average (percentile 25 – percentile 75).

and validated. Since the end of the nineties, several centers have used EuroSCORE to validate it.[11-13] In the United States, it was more accurate compared to other predictor models when validated in the database with more than 500.000 patients of the Society of Thorac Surgery.[14] However, a systematic review evaluating the performance of the EuroSCORE concluded that the model overestimates surgical risk based on five studies of different nationalities.[15] The present study corroborates the findings, finding unsatisfactory results for the predictive capacity of the evaluated scores, in contrast to a good performance of the locally adjusted model. The development of local risk scores presents growth, finding difficulties in implementation, but presenting progressive improvements and contributing to the identification of risk factors.[16-18] A recent body of results shows a better performance of models fitted with local data in relation to EuroSCORE, Parsonet Score and Ontario Risk Score.[19] Other studies in cardiovascular surgery suggest that most information on prognosis is contained in a few clinical variables, showing that simple models are as effective as complex models.[20] Although it is better suited than traditional scores, the score derived from the sample in this study is not intended for use in other services. Performing in only one center limits the external validity, where characteristics of the patients and the care body of the institution may vary.

Table 2 – Coefficients for adjusted models

Suitable model*	Odds Ratio (IC 95%)	Coefficient	Default error	p Value of the coefficient (Statistics Wald)
Previous myocardial revascularization	8.519 (1.026 - 59.381)	2.142	0.979	0.029
Previous creatinine	2.217 (0.815 - 6.018)	0.796	0.476	0.095
Age	1.081 (1.025 - 1.145)	0.077	0.028	0.006
FE ≤ 50	1.251 (0.360 – 3.617)	0.224	0.577	0.698
Vascular Brain Disease	1.398 (0.506 – 397.795)	2.637	1.489	0.077

** Constant Value for Model: -8,422; Default error: 1,955; p Value: < 0,001*

Conclusion

Risk scores in cardiovascular surgery should be revalidated locally and the development of simple local predictive models may present better results in a delimited environment.

Author contributions

Conception and design of the research: Viana VJC, Ribeiro NAM, Silva Junior AF. Acquisition of data: Viana VJC, Ribeiro NAM, Silva Junior AF. Analysis and interpretation of the data: Argolo FC, Correia LCL. Statistical analysis: Argolo FC. Writing of the manuscript: Viana VJC. Critical revision of the manuscript for intellectual content: Correia LCL.

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 Valcellos José da Cruz Viana, from Escola Bahiana de Medicina e Saúde Pública.

References

1. Asimakopoulos G, Al-Ruzzeh S, Ambler G, Omar RZ, Punjabi P. Amrani M, al. An evaluation of existing risk stratification models as a tool for comparison of surgical performances for coronary artery bypass grafting between institutions. Eur J Cardiothorac Surg. 2003;23(6):935-41.
2. Pikanem O, Niskanen M, Rehnberg S, Hippelainen M, Hynyem M. Intra-institutional prediction of outcome after cardiac surgery: comparison between a locally derived model and the EuroSCORE. Eur J Cardiothorac Surg. 2000;18(6):703-10
3. Nashef SA, Roques F, Michel P, Gauducheau E, Lemeshow S, Salamon R. European system for cardiac operative risk evaluation(EuroSCORE). Eur J Cardiothorac Surg. 1999;16(1):9-13.
4. Shahian MD, O'Brien SM, Filardo G, Ferraris VA, Haan CK, Rich JB, et al; Society of Thoracic Surgeons Quality Measurement Task Force. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 1 – coronary artery bypass grafting surgery. Ann Thorac Surg. 2009;88(1 Suppl):S2-22.

5. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kanel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97(18):1837-47.

6. Granger CB, Goldberg RJ, Dabbous O, Pieper KS, Eagle KA, Cannon CP, et al; Global Registry of Acute Coronary Events Investigators. Predictors of hospital mortality in the global registry of acute coronary events. Arch Intern Med. 2003,163(19):2345-53.

7. Smith LR, Harrel FE, Rankin JS, Califf RM, Pryor DB, Muhlbaier LH, et al. Determinants of early versus late cardiac death in patients undergoing coronary artery bypass graft surgery. Circulation. 1991;84(5 Suppl):III245-53.

8. Hosmer DW, Lemeshow S. Applied logistic regression. 2nd ed. New York: John Wiley and Sons; 2000.

9. Yan AT, Yan RT, Huynh T, Casanova A, Raimondo FE, Fitchett DH, et al; Canadian Acute Coronary Syndrome Registry 2 Investigators. Understanding physicians' risk stratification of acute coronary syndromes: insights from the Canadian ACS 2 Registry. Arch Intern Med. 2009;169(4):372-8.

10. Ivanov J, Tu JV, Naylor CD. Ready-made, recalibrated, or Remodeled? Issues in the use of risk indexes for assessing mortality after coronary artery bypass graft surgery. Circulation. 1999;99(16):2098-104.

11. Carvalho MR, Souza e Silva NA, Klein CH, Oliveira GM. Application of the EurSCORE in coronary artery bypass in public hospitals in Rio de Janeiro, Brazil. Rev Bras Cir Cardiovasc. 2010;25(2):209-17.

12. Yap CH, Reid C, Yii M, Rowland MA, Mohajeri M, Skillington PD, et al. Validation of the EuroSCORE model in Australia. Eur J Cardiothorac Surg. 2006;29(4):441-6.

13. Zheng Z, Li Y, Zhang S, Hu S; Chinese CABG registry Study. The Chinese coronary artery bypass grafting registry study: how well does the EuroSCORE predict operative risk for Chinese population? Eur J Cardiothorac Surg. 2009;35(1):54-8.

14. Geissler HJ, Holzl P, Marohl S, Kuhin-Regnier F, Mehlhorn U, Sudkanp M, et al. Risk stratification surgery: comparison of six score systems. Eur J Cardiothorac Surg. 2000;17(4):400-6.

15. Gogbashian A, Sedrakyan A, Treasure T. EurSCORE: a systematic review of international performance. Eur J Cardiothorac Surg. 2004;25(5):695-700. Erratum in: Eur J Cardiothorac Surg. 2004;26(2):463.

16. Gomes RV, Tura B, Mendonça Filho HT, Almeida Campos LA, Rouge A, Matos Nogueira PM, et al. A first postoperative day predictive score of mortality for cardiac surgery. Ann Thorac Cardiovasc Surg. 2007;13(3):159-64.

17. Cadore MP, Guaragna JC, Anacker JF, Albuquerque LC, Bodanese LC, Piccoli Jda C, et al. A score proposal to evaluate surgical risk in patients submitted to myocardial revascularization surgery. Rev Bras Cir Cardiovasc. 2010;25(4):447-56. Erratum in: Rev Bras Cir Cardiovasc. 2011;26(1):144.

18. Mejía OA, Lisboa LA, Puig LB, Moreira LF, Dallan LA, Pomerantzeff PM, et al. InsCor: a simple and accurate method for risk assessment in heart surgery. Arq Bras Cardiol. 2013;100(3):246-54.

19. Antunes PE. Eugenio L. Ferrão de Oliveira J. Antunes MJ. Mortality risk prediction in coronary surgery: a locally developed model outperforms external risk models. Interact Cardiovasc Thorac Surg. 2007;6(4):437-41.

20. Jones RH, Hannan EL, Hammermeister KE, Delong ER, O'Connor GT, Luepker RV, et al. Identification of preoperative variables needed for risk adjustment of short-term mortality after coronary artery bypass graft surgery. The Working Group Panel on the Cooperative CABG Database Project. J Am Coll Cardiol. 1996;28(6):1478-87.

International Journal of Cardiovascular Sciences. 2017;30(4):313-324

ORIGINAL ARTICLE

Are Body Fat and Uric Acid associated with Cardiovascular Risk Scores? Cross-Sectional Analysis in the PROCARDIO-UFV Trial

Juliane Soares Rodrigues, Alinne Paula de Almeida, Carla de Oliveira Barbosa Rosa, Helen Hermana Miranda Hermsdorff

Universidade Federal de Viçosa, Viçosa, MG – Brazil

Abstract

Background: Risk scores are tools used to indicate the probability of occurrence of a certain cardiovascular event and to previously identify individuals at low, medium, and high risk for the development of cardiovascular diseases.

Objective: To establish the cardiovascular risk of users of a cardiovascular health attention program of a university, and assess its association with lifestyle, clinical, sociodemographic data, and other cardiometabolic risk markers.

Methods: Cross-sectional study with a sample of 197 participants. Demographic, anthropometric, clinical, and metabolic data, eating habits and lifestyle information were collected using the Global Risk Score and the Framingham Risk Score. P-value < 0,05 was considered statistically significant.

Results: According to the Framingham Risk Score, 84% of the assessed population was considered low risk and 16% as intermediate/high risk. However, according to the Global Risk Score, 18% of the participants were low risk, 45% were intermediate risk and 37% were high risk for infarction or death from coronary heart disease in 10 years.

Conclusion: Excess body weight and uric acid serum levels showed to be significant cardiovascular risk markers in addition to those of the score and, consequently, they should be considered in clinical practice. (Int J Cardiovasc Sci. 2017;30(4):313-324)

Keywords: Cardiovascular Diseases/mortality; Obesity; Uric Acid; Life Style; Risk Factors.

Introduction

According to the World Health Organization (WHO), cardiovascular diseases (CVD) accounted for 33% of deaths in Brazil in 2011.[1] In Brazil, the cost of treating chronic arterial diseases has a large budgetary impact on the health sector. Moreover, it is known that Risk Factors (RF) have great influence on CVD onset.[2]

Therefore, over the years, several studies were carried out and, based on them, different Risk Scores (RS) were created. To prevent underestimation or overestimation of the individual's risk, some algorithms, based on regression analyses of population studies, have been created to identify individuals at low, medium, and high risk in advance.[3] In 1948, the Framingham Heart Study, of which objective was to identify the common factors or characteristics that contribute to CVD, led to the identification of the main RF for CVD: age, gender, systemic arterial hypertension (SAH), hypercholesterolemia, smoking, obesity, diabetes, and sedentary lifestyle.[4]

Another score used and recommended by the V Brazilian Guideline on Dyslipidemia and Atherosclerosis Prevention of 2013 is the Global Risk Score (GRS), which estimates the risk of myocardial infarction, cerebrovascular accident, peripheral vascular failure, or heart failure in 10 years.[5] RS are low-cost and easy-to-use tools because they estimate the risk based on simple, clinical, and laboratory variables routinely used in clinical practice.[6]

Mailing Address: Helen Hermana Miranda Hermsdorff
Universidade Federal de Viçosa, Departamento de Nutrição e Saúde. Avenida PH Rolfs s/n Campus Universitário. Postal Code: 36570-900, Viçosa, MG – Brazil
E-mail: helenhermana@ufv.br

DOI: 10.5935/2359-4802.20170060

Manuscript received October 31, 2016; revised manuscript February 24, 2017; accepted March 01, 2017.

From the nutritional point of view, it is important to identify the RF that influence CVD, to help with adequate diet intervention, both to prevent and treat them, whereas the RS allows an adequate intervention to improve the individual's metabolism, lipid profile, and lifestyle, which associated with dietary therapy, may reduce the incidence and prevalence of new cardiovascular events.[5]

The present study aimed to establish the cardiovascular risk of the users of a cardiovascular health care program of a university, as well as to evaluate their association with lifestyle, clinical, and sociodemographic factors and other cardiometabolic risk markers.

Methods

Subjects

This is a cross-sectional study, with data collection between November 2012 and March 2016, based on a subsample of the Cardiovascular Health Care Program of Universidade Federal de Viçosa (PROCARDIO-UFV). PROCARDIO-UFV is a program that promotes nutritional and cardiovascular health intervention and education to the UFV community. The program's inclusion criteria are: patients of both genders, age ≥ 20 years, being an UFV employee/employee's spouse or offspring or UFV student, having been diagnosed with CVD or occurrence of cardiometabolic RF, such as excess weight (Body Mass Index - BMI ≥ 25 kg / $m^{2)}$; hypertriglyceridemia (≥ 150 mg / dL); hypercholesterolemia (≥ 200 mg / dL), low HDL (men < 40 mg / dL and women < 50 mg / dL), blood pressure ≥ 130 / ≥ 85 mmHg or SAH diagnosis (systolic blood pressure - SBP ≥ 140 and / or Diastolic Blood Pressure - DBP ≥ 90 mmHg), fasting blood glucose ≥ 100 mg/dL or diagnosis of Diabetes Mellitus (DM) (fasting blood glucose ≥ 126 mg / dL) and / or medical referral. The program is registered in the Brazilian Registry of Clinical Trials (ReBEC) under the primary identifier RBR-5n4y2g.[7]

The data used were related to the first consultation. Of the 417 program users, 197 (116 women) were selected for having complete data on SBP, DBP, Total Cholesterol (TC), and fractions (HDL-c, LDL-C), triacylglycerols, age, presence or not of smoking and DM - all factors used in the evaluation of the assessed scores.

The study was approved by the UFV Ethics Committee on Human Research (Of. Ref. 066/2012/CEPH), on June 27, 2012, in accordance with Resolution 466/2012 of the National Health Council on research involving human beings. All subjects who agreed to participate in the study signed the Free and Informed Consent form, in accordance with the Helsinki Declaration principles.

Sociodemographic and lifestyle variables

Sociodemographic and lifestyle variables were collected through the patients' self-report and from medical records. Variables such as age, gender, marital status, and professional link with UFV were collected. Lifestyle variables included smoking (smokers or nonsmokers), regular physical activity (yes or no), and hours of sleep a day.

Anthropometric and body composition evaluation

Weight, height, and waist circumference were measured according to a protocol established in PROCARDIO-UFV.[8] BMI was calculated by dividing weight by squared height and classified according to the WHO criteria for adults.[9] For the elderly, the classification was made according to Lipschitz.[10] For the classification of abdominal obesity and cardiovascular risk, the criteria recommended by Alberti et al.[11], WC ≥ 80 cm for women and ≥ 90 cm for men, were used.

Percentage of Body Fat (%BF) (20/30 for men and women, respectively) was obtained through analysis of horizontal tetrapolar electrical bioimpedance (Biodynamics BIA 310 Model, Washington, USA), carried out with a standardized protocol.[12]

Biochemical and blood pressure evaluation

SBP and DBP levels were measured using a mechanical sphygmomanometer with a mercury column, according to the technique described in the VI Brazilian Hypertension Guidelines. SAH classification was also made according to the criteria of the VI Brazilian Hypertension Guidelines[13], with a cutoff point ≥ 140 and ≥ 90 mmHg.[13] The diagnosis of DM (fasting glycemia ≥ 126 mg / dL) followed the guidelines of the Report of The Expert Committee on Diagnosis and Classification of Diabetes Mellitus.[14]

For the metabolic evaluation, the following markers were analyzed: glucose, triacylglycerols, TC and fractions, Uric Acid (UA), platelets and leukocytes. LDL-c was calculated using Friedewald et al.'s equation.[15] The criteria of the V Brazilian Guidelines for Dyslipidemia and Prevention of Atherosclerosis and the National Cholesterol Education Program's

Adult Treatment Panel III (NCEP-ATP III) were used to classify these variables.[5]

Food survey assessment

The volunteers answered a questionnaire about food habits, in which they were asked about the consumption of salt (little, normal, too much), fat (type of fat consumed) and alcohol.

Risk stratification

The present study used the Framingham Risk Score (FRS) and the GRS stratification, according to the IV and V Brazilian Guidelines for Dyslipidemias and Prevention of Atherosclerosis, respectively.[3,5]

The values of TC and HDL-c for the classification of dyslipidemias were defined according to the V Brazilian Guideline on Dyslipidemias and Prevention of Atherosclerosis.[5] Individuals were considered smokers when they self-reported smoking.

Global Risk Score

The variables associated to the risk of developing CVD that were incorporated into the GRS are: SBP, smoking, TC, HDL-c, glucose intolerance, gender, and age. For the classification of PROCARDIO-UFV users according to the GRS, the following criteria were used: age (zero to +15 and zero to +12 points, respectively, for men and women), HDL-c (-2 to +2 points), TC (zero to +4 and zero to +5 points, respectively, for men and women), untreated SBP (-2 to +3 points and -3 to +5 points respectively for men and women), treated SBP (zero to +5 points and -1 to +7, respectively, for men and women), smoking (zero to +4 points and zero to +3 points respectively for men and women) and diabetes (zero to +3 points and zero to +4 points, respectively, for men and women).

According to the sum of the points obtained, each subject was assigned a percentage probability of having cardiovascular events. Individuals whose probability of having major cardiovascular events (coronary artery disease, cerebrovascular disease, peripheral obstructive arterial disease, or heart failure) in 10 years was less than 5% were considered as low risk. Those who were classified in this category and who reported a family history of premature CVD were reclassified to intermediate risk. Men with a calculated risk ≥ 5% and ≤ 20% and women with calculated risk ≥ 5% and ≤ 10% of occurrence of any of the aforementioned events were considered as intermediate risk. Those with a calculated risk > 20% for men and > 10% for women over a 10-year period were considered as high risk.[5]

Framingham Risk Score

The assignment of points according to the FRS occurred according to the criteria of the Brazilian Society of Cardiology (SBC).[3]

For the classification of users of PROCARDIO-UFV using the FRS, age (-9 to +13 and -7 to +16 points, respectively, for men and women), TC (zero to +11 and zero to +13 for men and women, respectively), smoking (zero to +8 and zero to +9 points, for men and women respectively), HDL-c (-1 to 2 points for men and women) and untreated SBP (zero to 2 and zero to +4 points, respectively, for men and women) and treated SBP (zero to +3 and zero to +6 points, respectively, for men and women).

In the second phase of the calculation, after these steps, the points acquired were added up and the absolute risk in 10 years was obtained. Men who scored < 0 to 12 points were classified as low risk (< 10%); as intermediate risk (≥ 10% ≤ 20%) those who scored 13 to 15 points; and high risk (> 20%) those who scored more than 16 points. Women who scored < 9 to 19 points were classified as low risk (< 10%); as intermediate risk (≥ 10% ≤ 20%) those who scored 20 to 22 points; and high risk (> 20%) those who scored more than 23 points.

Statistical analysis

Data were shown as mean ± standard deviation, or as median (25^{th} and 75^{th} percentiles), according to the normality of each variable, which was evaluated by the Kolmogorov-Smirnov normality test. The unpaired Student's t tests and Analysis of Variance (ANOVA) followed by Tukey's post hoc were used to compare the variables between the groups according to normality and the number of comparison groups. The chi-square test was used for comparison of frequencies. Statistical analyses were performed using the Statistical Package for Social Sciences (SSPS), version 20.0, and the level of statistical significance was set at 5%.

The categorical variables were shown, as follows: professional link with the UFV (employee, student or family member); marital status (single, married, widowed or divorced); hypercholesterolemia if CT

≥ 200 mg / dL (yes or no); hypertriglyceridemia if TG ≥ 150 mg/dL (yes or no); diabetes if fasting glycemia ≥ 126 mg / dL (yes or no); SAH if blood pressure ≥ 130 and ≥ 85 mmHg (yes or no); physical activity (yes or no); smoking (never smoked, used to smoke, yes); alcohol (never drink, drink occasionally, drink every day, others); salt consumption (normal, little, a lot, not reported); use of fat (lard, vegetable oil, all options); and hours of sleep (not reported, ≤ 4 hours, 4 to 6 hours, 6 to 8 hours, ≥ 8 hours).

Results

In our sample, 58.9% of the subjects were females (Tables 1 and 2). According to the calculated FRS, 16% of the population was of intermediate/high risk. However, according to the FRS, 37% of the population was at high risk of infarction or death from coronary disease in 10 years.

The median age for individuals with low risk at the FRS was 38 years (25-53) and for intermediate /high risk, 60 years (56.2-67.7) with $p < 0.001$. In the GRS, the low risk group was 37 years (32 to 44); intermediate risk, 52 years (48 to 57); and high risk, 60 years (55 to 65), with $p < 0.001$. As for the professional link with the university, in the FRS 100% of the students were classified as low risk ($p < 0.05$), but the GRS showed that 50% were in the high-risk group ($p < 0.05$). Regarding university employees, 39.1% were classified as intermediate / high risk according to the FRS and 49.2% as high risk according to the GRS. Regarding SAH, according to the FRS, 25.9% of the individuals who were hypertensive were classified as intermediate/ high risk, and according to the GRS, 51.5% were classified as high risk ($p < 0.05$).

The median fasting glycemia (mg/dL), according to the FRS for the individuals classified as intermediate / high risk, was 99.5 (91 to 115) and in the GRS, 106 (96 to 126) for high risk ($p < 0.05$). As for triglycerides (mg/dL), according to the FRS, the median values were 156.5 (119.3 to 252.7) for individuals at intermediate/high risk and, in the GRS, 151 (117.3 to 227.5) for individuals at high risk ($p < 0.05$). UA values were significantly high in the intermediate/high risk groups in both scores. The mean and standard deviation of the UA values (mg / dL) in the intermediate / high risk group according to the FRS were 5.4 ± 1.4 and according to the GRS, they were 5.0 ± 1.2 for the high group. In the GRS, 81.3% of diabetics were classified as high risk ($p <0.05$) ($p < 0,05$) (Tables 1 and 2).

Tables 3 and 4 are related to lifestyle and show that, according to the FRS, 30% of the smokers were classified as intermediate / high risk, and among those who smoked, 33.3% were also included in this risk group ($p < 0.05$). According to the GRS, 80% of the individuals who smoked were classified as high risk, and among those who used to smoke, 47.1% were classified as high risk ($p < 0.05$). Regarding the use of fats in FRS, 86% of the individuals using vegetable oil were classified as low risk ($p < 0.05$).

Regarding the nutritional status, among those classified according to the FRS as intermediate/high risk, 72.1% had excess weight (BMI ≥ 25 kg/m²), whereas in the GRS, 80.9% of individuals with excess weight were classified as high risk. Regarding abdominal obesity (WC ≥ 88/102 cm for women and men, respectively), in the FRS, 96.9% of the subjects were classified as intermediate/high risk, whereas in the GRS, 95.7% of those classified as high risk had abdominal obesity. Considering the excess body fat (BF% > 20/30 for men and women, respectively), a prevalence of 76.9% was found in the individuals in the intermediate / high risk group of the FRS and 71.4% in the GRS.

In the intermediate / high risk group of the FRS, the mean and standard deviation of the BMI (kg/m²) were higher when compared with the low-risk group ($p < 0.05$). According to this same score, BF% was also higher in the intermediate/high risk group, when compared to the low risk group ($p < 0.05$). In the high-risk group of the GRS, the mean WC was higher when compared to the other groups ($p < 0.05$). (Table 5)

Discussion

To know the prevalence of RF and assess the overall risk of developing CVD are crucial for effective prevention with the correct definition of therapeutic goals, aiming to minimize risks and maximize benefits.[16]

When comparing the risk stratification between the scores, it was observed that the risk distribution was higher in the GRS, whereas in the FRS, the number of individuals classified as low risk was very high, a fact that was also identified in the study by Oliveira et al.[17]

The FRS was carried out with measures of almost half a century ago. Therefore, there is a real possibility that the risk has changed over time. Moreover, the absolute risk of the participants in the Framingham study (North-American) is not necessarily the same as in other populations.[4]

Table 1 – Demographic, clinical, and lifestyle characteristics, according to the Framingham Risk Score

Variables	Framingham Risk Score		*p* value
	Low risk (n = 165)	Intermediate/high risk (n = 32)	
Gender, n (%)			
Male	56 (69.3)	25 (30.7)	< 0.001*
Female	109 (93.9)	7 (6.1)	
Age, years	38 (25-53)	60 (56-68)	< 0.001*
Professional link, n (%)			
Employee	42 (60.9)	27 (39.1)	
Student	79 (100)	–	< 0.001*
Family member	43 (89.6)	5 (10.4)	
Marital status, n (%)			
Single	78 (97.5)	2 (2.5)	
Married	73 (72.3)	28 (27.7)	0.028*
Widowed	6 (85.7)	1 (14.3)	
Divorced	6 (85.7)	1 (14.3)	
Hypercholesterolemia (TC ≥ 200 mg/dL)			
Yes	86 (81.9)	19 (18.1)	0.453
No	79 (85.9)	13 (14.1)	
Hypertriglyceridemia (TG ≥ 150 mg/dL)			
Sim	67 (80.7)	16 (19.3)	0.296
Não	89 (86.4)	14 (13.6)	
Diabetes (fasting glucose ≥ 126 mg/dL)			
Yes	11 (68.7)	5 (31.3)	0.089
No	144 (85.2)	25 (14.8)	
Arterial hypertension (BP ≥ 130 and ≥ 85 mmHg)			
Yes	57 (74.1)	20 (25.9)	0.003*
No	108 (90)	12 (10)	
Fasting glucose, mg/dL	89 (81-100)	99.5 (91-115)	0.004*
TC/HDL ratio	4.1 (3.4-4.9)	5.0 (4.0-6.0)	0.017*
LDL/HDL ratio	2.6 ± 1.0	3.2 ± 1.5	0.021*
Triglycerides, mg/dL	138.5 (100-199.7)	156.5 (119.3-252.7)	0.033*
Uric acid, mg/dL	4.4 ± 1.6	5.4 ± 1.4	0.001*
Leukocytes, mm^3	6.382.9 ± 1.673.6	6.201.4 ± 1.661.1	0.601
Platelets, mm^3	248.9 ± 51.8	239.72 ± 53.3	0.391

Data shown as mean (standard deviation), median, 25th and 75th percentiles, and frequencies; P value using Student's t-test or chi-square test.
** p < 0.05. TC: total cholesterol; TG: triglycerides; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein.*

Table 2 – Demographic, clinical and lifestyle characteristics, according to the Global Risk Score

Variables	Global Risk Score			*p* value
	Low risk (n = 23)	Intermediate risk (n = 56)	High risk (n = 47)	
Gender, n (%)				
Male	6 (10.2)	27 (45.8)	26 (44.06)	0.031
Female	17 (25.4)	29 (43.3)	21 (31.34)	
Age, years	37 (32-44)[a]	52 (48-57)[b]	60 (55-65)[c]	< 0.001*
Professional link, n (%)				
Employee	5 (7.7)	28 (43.1)	32 (49.2)	
Student	9 (50)	9 (50)	–	0.040*
Family member	9 (21.4)	18 (42.9)	15 (35.7)	
Marital status, n (%)				
Single	10 (52.6)	7 (36.9)	2 (10.5)	
Married	12 (13.0)	42 (45.1)	39 (41.9)	0.043*
Widowed	1 (14.2)	3 (42.9)	3 (42.9)	
Divorced	–	4 (57.1)	3 (42.9)	
Hypercholesterolemia (TC ≥ 200 mg/dL)				
Yes	9 (14.5)	30 (48.4)	23 (37.1)	0.590
No	14 (21.9)	26 (40.6)	24 (37.5)	
Hypertriglyceridemia (TG ≥ 150 mg/dL)				
Yes	14 (26.9)	15 (28.9)	23 (44.2)	0.980
No	9 (13.2)	38 (55.9)	21 (30.9)	
Diabetes (fasting glucose ≥ 126 mg/dL)				
Yes	–	3 (18.7)[a]	13 (81.3)[b]	< 0.001*
No	23 (20.9)	53 (48.2)	34 (30.9)	
Arterial hypertension (BP ≥ 130 and ≥ 85 mmHg)				
Yes	8 (12.1)	24 (36.4)	34 (51.5)	0.001*
No	15 (25)	32 (53.3)	13 (21.7)	
Fasting glucose, mg/dL	89 (81-96)[a]	92 (85.2-102.5)[b]	106 (96-126)[c]	< 0.001*
TC/HDL ratio	4.4 (3.2-5)	4.1 (3.5-5.4)	4.6 (3.6-5.5)	0.390
LDL/HDL ratio	2.7 ± 1.1	2.8 ± 0.9	2.9 ± 1.4	0.495
Triglycerides, mg/dL	168 (112-214)	120 (91.5-189.5)	151 (117.3-227.5)	0.091
Uric acid, mg/dL	4.3 ± 1.0[a]	4.2 ± 1.5[b]	5.0 ± 1.2[b]	0.016*
Leukocytes, mm^3	7.004.5 ± 1.636.3[a]	6.055.6 ± 1.640.5[b]	5.888.2 ± 1.517.3[a,b]	0.028*
Platelets, mm^3	247.0 ± 54.2	235.2 ± 48.7	246.8 ± 52.4	0.521

*Data are shown as mean (standard deviation), median, 25th percentile and 75th percentile and frequencies. Value of p through Analysis of Variance (ANOVA) or chi-square test. Letters a, b, and c: median / mean followed by different letters on the same line differ from each other at Tukey's test at the 5% probability level. * p < 0.05. TC: total cholesterol; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein.*

Table 3 – Lifestyle and food variables according to the Framingham Risk Score

Variable	Framingham Risk Score		*p* value
	Low Risk (n=165)	Intermediate/High risk (n=32)	
Physical activity, n (%)			
Yes	91 (88.3)	12 (11.7)	0.093
No	74 (79.6)	19 (20.4)	
Smoking status, n (%)			
Never smoked	120 (92.3)	10 (7.7)	
Ex-smoker	38 (66.7)	19 (33.3)	< 0.001*
Smoker	7 (70.0)	3 (30.0)	
Alcohol consumption, n (%)			
Never drinks alcohol	64 (85.3)	11 (14.7)	
Drinks sporadically	93 (83.8)	18 (16.2)	0.289
Drinks everyday	3 (50)	3 (50)	
Other	1 (100)	–	
Salt consumption n (%)			
Normal	85 (85)	15 (15)	
Little	52 (82.5)	11 (17.5)	0.529
A lot	23 (79.3)	6 (10.7)	
Did not report	1 (100)	–	
Use of fats/oils, n (%)			
Lard	1 (100)	–	
Vegetable oil	153 (86.0)	25 (14.0)	0.001*
All options	7 (50)	7 (50)	
Hours of sleep, n (%)			
Did not report	1 (50)	1 (50)	
≤ 4	19 (95)	1 (5)	
4-6	134 (83.2)	27 (16.8)	0.357
6-8	3 (60)	2 (40)	
≥ 8	4 (80)	1 (20)	

Data shown as frequencies. P value using Student's t-test or chi-square test.

Both scores showed an evident association between age and coronary risk. The increase in both variables was proportional, which indicates the need to establish earlier and more frequent health promotion and prevention actions for cardiovascular diseases for the at-risk population, considering the trend towards increased life expectancy and the resulting greater possibility of exposure to RF for CVD.[18]

The GRS and the FRS allowed a better visualization of variables related to the risk of developing coronary diseases in 10 years, making it essential to identify

individuals exposed to cardiovascular risk as a target group for preventive cardiovascular actions at the individual and population levels.[19]

Increased levels of physical activity and specific dietary changes should be encouraged.[20] Nutritional interventions are effective in helping to reduce cardiovascular events in high-risk individuals. Protective diets are based on foods of plant origin in abundance (fruits, vegetables, whole grains, legumes, nuts, and others), olive oil and other vegetable oils as the main source of fat.[21]

Table 4 – Lifestyle and food variables, according to the Global Risk Score

Variable	Global Risk Score			*p* value
	Low risk (n = 23)	Intermediate risk (n = 56)	High risk (n = 47)	
Physical activity, n (%)				
Yes	13 (19.7)	31 (47.0)	22 (33.3)	0.436
No	10 (16.9)	25 (42.4)	24 (40.7)	
Smoking status, n (%)				
Never smoked	18 (25.7)	33 (47.2)	19 (27.1)	
Ex-smoker	5 (9.8)	22 (43.1)	24 (47.1)	0.001*
Smoker	–	1 (20)	4 (80)	
Alcohol consumption. n (%)				
Never drinks alcohol	21.7 (13)	41.7 (25)	36.7 (22)	
Drinks sporadically	16.9 (10)	45.8 (27)	37.3 (22)	0.360
Drinks everyday	–	1 (25)	3 (75)	
Other	–	1 (100)	–	
Salt consumption. n (%)				
Normal	9 (16.4)	25 (45.4)	21 (38.2)	
Little	10 (20)	24 (48)	16 (32)	0.932
A lot	4 (22.2)	5 (27.8)	9 (50)	
Not reported	–	1 (100)	–	
Use of oils/fats. n (%)				
Lard	100 (1)	–	–	
Vegetable oil	19 (17.4)	51 (46.8)	39 (35.8)	0.195
All options	3 (21.4)	3 (21.4)	8(57.2)	
Hours of sleep. n (%)				
Not reported	–	1 (50)	1 (50)	
≤ 4	1 (8.3)	6 (50)	5 (41.7)	
4-6	22 (21.4)	43 (41.7)	38 (36.9)	0.915
6-8	–	2 (50)	2 (50)	
≥ 8	–	1 (50)	1 (50)	

*Data shown as frequencies. P value using chi-square test. * p <0.05.*

Table 5 – Nutritional status according to cardiovascular risk scores

Variables	Framingham Risk Score		*p* value
	Low risk (n = 165)	Intermediate/high risk (n = 32)	
BMI (kg/m²)	28.8 ± 5.8	31.0 ± 5.2	0.048*
Body fat (%)	30.7 ± 7.9	31.5 ± 7.1	< 0.001*
Waist circumference (cm)	95.6 ± 14.5	107.7 ± 13.0	0.621

Variables	Global Risk Score			*p* value
	Low risk (n=23)	Intermediate risk (n=56)	High risk (n=47)	
BMI (kg/m²)	30.3 ± 5.9	29.4 ± 4.4	31.4 ± 5.8	0.182
Body fat (%)	32.6 ± 7.3	30.6 ± 8.0	32.7 ± 7.8	0.436
Waist circumference (cm)	99.9 ± 15.2[a]	99.3 ± 11.6[b]	106.1 ± 13.4[c]	0.025*

*Data are shown as mean (standard deviation). P value using Student's t-test and Analysis of Variance (ANOVA). Median / mean followed by the same letter, in the same line, do not differ from each other at Tukey's test at the 5% probability level. * p < 0.05. BMI: body mass index.*

Moreover, higher values of BMI, %BF and WC were found in subjects with intermediate / high risk in both scores. According to Barbosa et al., the increase in morbidity and mortality due to chronic-degenerative diseases is associated with excess weight and fat deposits (mainly abdominal fat), favoring the occurrence of cardiovascular events - particularly coronary events.[22] A study by Casanueva et al.[23] showed that CVD frequency increased in parallel with increased adiposity measured by BMI or WC. Moreover, abdominal obesity has been strongly associated with dyslipidemia and SAH.[24]

Ademais et al.[25] found that the occurrence of obesity due to BMI and %BF was significantly higher in those individuals with a hypertriglyceridemic waist phenotype. Hermsdorff et al.[26] found that individuals with higher WC and waist-to-hip ratio had higher concentrations of C-reactive protein (CRP), complement C3, interleukin 6 (IL6) and retinol-binding protein ($p < 0.05$).

In another study,[27] the individuals with the highest tertiles of trunk fat and WC had the highest concentrations of CRP and IL6, in addition to higher values of blood pressure, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) and LDL/HDL-c ratio ($p < 0.05$) – factors that, when associated, increase the chances for CVD.

In both scores, the presence of high values of fasting glycemia and SAH showed an increase that was proportional to the risk. The so-called "visceral obesity" is associated with a higher mortality rate than peripheral obesity. This difference is due to the fact that visceral adipose tissue is metabolically more active than subcutaneous adipose tissue, causing, for instance, a high production of glucose and, consequently, type 2 DM and hyperinsulinemia. This higher secretion of insulin causes sodium retention, resulting in SAH.[28]

Interestingly, we found that in both the FRS and GRS, UA values were increased, as they developed from the RS. The acute increase in UA levels seems to be a protective factor to oxidative stress, and its chronic increase is associated with the risk of chronic noncommunicable diseases.[29] Hyperuricemia has been associated with the occurrence of metabolic syndrome, which is recognized as an important cardiovascular RF. However, the use of UA has been commonly ignored in clinical practice and in the context of RF; its inclusion as a variable for cardiovascular risk stratification may be interesting, since it is an easy-to-perform and low-cost exam that is useful in clinical practice.[8,30]

In the GRS, slightly more than half of the individuals with SAH were classified as high risk, which may be justified by its important association with the development of coronary diseases, mainly due to social and physical factors (educational level, elevated TC levels, and DM), which are frequently associated with SAH. Because there is a strong relationship with lifestyle, this disease can be prevented, reduced, or treated by adopting healthy life habits.[31]

Despite the low rate of smoking in the present study, smoking was significantly associated with coronary risk in both scores. It is known that smoking is a significant modifiable cardiovascular RF in the world's population.[29] According to Weiner et al.[32], approximately one in five CVD deaths are caused by smoking, which, alone, doubles the possibility of the disease and, when associated with TC or HAS, this risk is multiplied by four (it becomes eight-fold higher when all three factors are combined).

The present study has limitations. As a cross-sectional study, it is not possible to infer a cause-effect association for the results. Furthermore, to calculate the scores, a group of variables was necessary, which were not always available in the medical records of all users. However, in the literature, few Brazilian studies perform the calculation of these scores to identify risk in patients with cardiometabolic risk.

Conclusion

The scores showed a difference in the risk distribution. Excess body weight and uric acid values were shown to be important markers of cardiovascular risk in addition to those present in the score. The need for further research on the subject and the development of more specific risk scores for each population was evident.

Acknowledgements

We thank the users of PROCARDIO-UFV, who allowed their data to be used in the study, the professionals and the voluntary trainees of the program. We would also like to thank the Pro-Rectory of Extension and Culture (PEC/UFV), for the university extension grant given to JS Rodrigues, and Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), for the grant given to AP Almeida. HHM Hermsdorff is a Research Productivity Fellow of Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

Author contributions

Conception and design of the research: Hermsdorff HHM. Acquisition of data: Rodrigues JS, Almeida AP, Hermsdorff HHM. Analysis and interpretation of the data: Rodrigues JS, Almeida AP, Hermsdorff HHM. Statistical analysis: Rodrigues JS, Almeida AP, Hermsdorff HHM. Writing of the manuscript: Rodrigues JS, Almeida AP. Critical revision of the manuscript for intellectual content: Almeida AP, Rosa COB, Hermsdorff HHM.

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 Conclusion of the Nutrition Course by Juliane Soares Rodrigues, from Universidade Federal de Viçosa.

References

1. Soares TS, Piovesan CH, Gustavo Ada S, Macagnan FE, Bodanese LC, Feoli AM. Alimentary habits, physical actitivy, and Framingham global risk score in metabolic syndrome. Arq Bras Cardiol. 2014;102(4):374-82.
2. Andrade JP, Piva e Mattos LA, Carvalho AC, Machado CA, Oliveira GM. National physician qualification program in cardiovascular disease prevention and integral care. Arq Bras Cardiol. 2013;100(3):203-11.
3. Sposito AC, Caramelli B, Fonseca FA, Bertolami MC, Afiune Neto A, Souza AD, et al. [IV Brazilian Guideline for dyslipidemia and atherosclerosis prevention: Department of Atherosclerosis of Brazilian Society of Cardiology]. Arq Bras Cardiol. 2007;88 Suppl 1:2-19.
4. Lotufo PA. O escore de risco de Framingham para doenças cardiovasculares. Rev Med (São Paulo). 2008;87(4):232-7.
5. Xavier HT, Izar MC, Faria Neto JR, Assad MH, Rocha VZ, Sposito AC, et al; Sociedade Brasileira de Cardiologia. [V Brazilian Guidelines on Dyslipidemias and Prevention of Atherosclerosis]. Arq Bras Cardiol. 2013;101(4 Suppl 1):1-20.
6. Sampaio MR, Melo MB, Wanderley MS. Overall Cardiovascular Risk Stratification in Patients Enrolled at a Family Health Unit (USF) Maceió, Alagoas state, Brazil. Rev Bras Cardiol. 2010;23(1):47-56.
7. Registro Brasileiro de Ensaios Clínicos. [Internet]. Aplicação de diferentes estratégias de terapia nutricional no Programa de Atenção à Saúde Cardiovascular – PROCARDIO-UFV. RBR-5n4y2g. [Acesso em 2014 ago 8]. Disponível em: http://www.ensaiosclinicos.gov.br/rg/RBR-5n4y2g
8. Silva HA, Carraro JC, Bressan J, Hermsdorff HH. Relation between uric acid and metabolic syndrome in subjects with cardiometabolic risk. Einstein. 2015;13(2):202-8.
9. World Health Organization.(WHO). BMI Classification. Genéve; 2013.
10. Lipschitz DA. Screening for nutritional status in the elderly. Prim Care. 1994;21(1):55-67.
11. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al; International Diabetes Federation Task Force on Epidemiology and

Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation.; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009;120(16):1640-5.

12. Vasquez AC, Rosado LE, Rosado GP, Ribeiro RC, Franceschini SC, Geloneze B, et al. Predictive ability of anthropometric and body composition indicators in the identification of insulin resistance. Arq Bras Endocrinol Metab. 2009;53(1):72-9.

13. Sociedade Brasileira de Cardiologia, Sociedade Brasileira de Hipertensão, Sociedade Brasileira de Nefrologia. [VI Brazilian Guidelines on Hypertension]. Arq Bras Cardiol. 2010;95(1 Suppl):1-51. Erratum in: Arq Bras Cardiol. 2010;95(4):553.

14. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 1997;20(7):1183-97.

15. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem. 1972;18(6):499-502.

16. Mascarenhas CH, Reis LA, Souza MS. Avaliação do risco de doença coronariana em adultos e idosos no município de Lagêdo do Tabocal / BA. Arq Ciênc Saúde Unipar. 2009;13(1):15-20.

17. Oliveira AC, Ferreira RC, Santos AA. Cardiovascular risk assessment according to the Framingham score and abdominal obesity in individuals seen by a clinical school of nutrition. Rev Assoc Med Bras (1992). 2016;62(2):138-44.

18. Silva VR, Cade NV, Molina MC. Risco coronariano e fatores associados em hipertensos de uma Unidade de Saúde da Família. Rev Enferm UERJ. 2012;20(4):439-44.

19. Schaan BD, Harzheim E, Gus I. Cardiac risk profile in diabetes mellitus and impaired fasting glucose. Rev Saude Publica. 2004;38(4):529-36.

20. Block G, Azar KM, Romanelli RJ, Block TJ, Hopkins D, Carpenter HA, et al. Diabetes prevention and weight loss with a fully automated behavioral intervention by email, Web, and mobile phone: a randomized controlled trial among persons with prediabetes. J Med Internet Res. 2015;17(10):e240.

21. Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Atenção Básica. Prevenção clínica de doenças cardiovasculares, cerebrovasculares e renais. Brasília;2006.

22. Barbosa LS, Scala LC, Ferreira MG. Association between anthropometric markers of body adiposity and hypertension in an adult population of Cuiabá, Mato Grosso. Rev Bras Epidemiol. 2009;12(2):237-47.

23. Casanueva FF, Moreno B, Rodríguez-Azeredo R, Massien C, Conthe P, Formiguera X, et al. Relationship of abdominal obesity with cardiovascular disease, diabetes and hyperlipidaemia in Spain. Clin Endocrinol (Oxf). 2010;73(1):35-40.

24. Oliveira AC, Ferreira RC, Santos, AA. Cardiovascular risk assessment according to the Framingham score and abdominal obesity in individuals seen by a clinical school of nutrition. Rev Assoc Med Bras (1992). 2016;62(2):138-44.

25. Oliveira JL, Lopes LL, Pelúzio MC, Hermsdorff HH. Hypertriglyceridemic waist phenotype and cardiometabolic risk in dyslipidemic subjects. Rev Bras Cardiol. 2014;27(6):395-402.

26. Hermsdorff HH, Zulet MA, Puchau B, Martinez JA. Central adiposity rather than total adiposity measurements are specifically involved in the inflammatory status from healthy young adults. Inflammation. 2011;34(3):161-70.

27. Hermsdorff HHM, Puchau B, Zulet MA, Martinez JA. Association of body fat distribution with proinflammatory gene expression in peripheral blood mononuclear cells from young adult subjects. OMICS. 2010;14(3):297-307.

28. Sugerman HJ. The pathophysiology of severe obesity and the effects of surgically induced weight loss. Surg Obes Relat Dis. 2005;1(2):109-19.

29. Gaffo AL, Edwards NL, Saag KG. Gout. Hyperuricemia and cardiovascular disease: how strong is the evidence for a causal link? Arthritis Res Ther. 2009;11(4):240.

30. de Oliveira A, Miranda Hermsdorff HH, Guedes Cocate P, Bressan J, Azevedo Novello A, Cardoso dos Santos E, et al. The impact of serum uric acid on the diagnostic of metabolic syndrome in apparently healthy Brazilian middle-aged men. Nutr Hosp. 2014;30(3):562-9.

31. Miranzi SS, Ferreira FS, Iwamoto HH, Pereira GA, Miranzi MA. Qualidade de vida de indivíduos com diabetes mellitus e hipertensão acompanhados por uma equipe de saúde da família. Texto Contexto Enferm. 2008;17(4):672-9.

32. Weiner P, Waizman J, Weiner M, Rabner M, Magadle R, Zamir D. Smoking and first acute myocardial infarction: age, mortality and smoking cessation rate. Isr Med Assoc J. 2000;2(6):446-9.

International Journal of Cardiovascular Sciences. 2017;30(4):325-333

ORIGINAL ARTICLE

Green Tea Attenuates Hypotension Induced by Physical Exercise: A Randomized, Placebo Controlled Study

Manoel Miranda Neto, Raquel Suelen Brito da Silva, Taís Feitosa da Silva, Fabiano Ferreira de Lima, Alexandre Sérgio Silva

Universidade Federal da Paraíba (UFPB), João Pessoa, PB – Brazil

Abstract

Background: Studies have shown that chronic administration of green tea decreases blood pressure (BP) at rest, while a single exercise session also promotes reduction of BP.

Objective: To investigate whether if a single dose of green tea prior to aerobic exercise session improves post-exercise hypotension (PEH).

Methods: Randomized, double-blind, placebo controlled study. Fifteen hypertensive patients (53 ± 3.3 years) participated in two study sessions: green tea+exercise (GTE) and placebo+exercise (PLE). Thirty minutes after ingesting 2 g of green tea or placebo, they performed 60 minutes of treadmill walking at 60 to 85% of maximum heart rate. BP was measured at rest and at every 10 minutes after exercise for 60 minutes. Blood samples were taken before ingestion of green tea or placebo and immediately after exercise to determine malondialdehyde (MDA) and nitrite (NO) concentrations.

Results: On PLE day, systolic PEH was detected at all post-exercise time points (BP reduction by 6.5-11.8 mmHg), whereas on GTE day, PEH was found only at 20 and 40 minutes post-exercise (BP reduction by 5.9 and 5.8 mmHg, respectively). BP reduction was significantly higher in PLE at 10, 20 and 30 minutes post-exercise compared with GTE. In addition, GTE resulted in hypertensive diastolic response, while on PLE day, diastolic PEH was seen only at 20 minutes post-exercise. No changes in MDA or NO concentrations in response to exercise were observed.

Conclusion: Green tea supplementation prior to an aerobic exercise session attenuated systolic PEH and induced diastolic hypertensive response to aerobic exercise in hypertensive patients. (Int J Cardiovasc Sci. 2017;30(4):325-333)

Keywords: Camellia sinensis / drug effects; Hypotension; Exercise; Oxidative Stress; Antioxidants.

Introduction

It is known that a single bout of aerobic exercise can promote significant and clinically relevant reduction in blood pressure (BP) in hypertensive subjects.[1] This phenomenon is called post-exercise hypotension (PEH). The magnitude and duration of PEH are dependent of intensity and duration of the exercise.[2] However, other factors may influence PEH, such as genetic characteristics[3] and initial blood pressure level. Our group has tested the influence of food on PEH and found that isolated caffeine[4] or coffee intake before or after exercise,[5] abolished hypotension induced by a session of aerobic exercise in hypertensive patients.

Previous studies[6-9] have shown that green tea, despite containing caffeine, promotes reduction of resting BP. This effect can be explained by the high antioxidant and anti-inflammatory capacity of catechins.[7] However, one cannot disregard the presence of caffeine in green tea, and the possibility that isolated intakes of the beverage result in vasoconstriction and elevation of BP at rest, or attenuation of PEH, similarly to what has been reported with coffee.[4,5]

So far, it is unknown whether the consumption of green tea can alleviate PEH or optimize exercise-induced BP reduction due to the presence of antioxidants. Thus, this study was conducted to verify the effect of a

Mailing Address: Alexandre Sérgio Silva
Rua Silvino Lopes, 410, apto 804. Postal Code: 58039-190, Tambaú, João Pessoa, PB – Brazil
E-mail: alexandresergiosilva@yahoo.com.br, ass974@yahoo.com.br

DOI: 10.5935/2359-4802.20170062

Manuscript received January 23, 2017, revised manuscript March 11, 2017, accepted March 15, 2017.

single dose of green tea before an aerobic exercise session on BP and oxidative stress response in hypertensive middle-aged adults.

Methods

Subjects

This was a randomized, double-blind, placebo-controlled study, performed on fifteen hypertensive individuals (8 women) aged 53 ± 3.3 years. These subjects were physically active at least 3 months prior to the trial. This sample size was determined based on previous studies in which hypertensive individuals have experienced the phenomenon of PEH.[10-12] All patients used anti-hypertensive medications and maintained medication throughout the study period. Diabetic subjects and menopaused women were excluded from the study.

The study was approved by the Human Research Ethics Committee of the Health Sciences Centre of the Federal University of Paraiba (identification number 0120/13). All participants signed the informed consent form, according to the National Health Council resolution (no. 466/12).

Study design

Each subject participated in two experiments, performed on two days separated by 48 hours. Experiments were conducted in the afternoon always at the same time. On each day, each participant received one dose of green tea (GTE, green tea + exercise) or placebo (PLE, placebo + exercise) 30 minutes before the aerobic exercise protocol. Heart rate was measured at rest and in every ten minutes during exercise. BP measurements were taken before (at rest), immediately after exercise and in every ten minutes during the 60-minute recovery period after the exercise. Blood samples were collected prior and immediately after exercise for analysis of plasmatic concentration of nitrite (NO) and malondialdehyde (MDA). The experiment protocol is shown in Figure 1.

Physical exercise

Aerobic exercise program consisted of 60-minute of treadmill walking at 60% to 85% of maximum heart rate.[13] Heart rate was monitored using a Polar heart rate monitor (Polar RS800CX, Polar ElectroOy, Kempele, Finland). Furthermore, exercise should be performed at intensity between 11 and 14 on Borg and Noble's 6-20 perceived exertion scale.[14]

Supplementation of green tea or placebo

Green tea and placebo capsules were produced in a compounding laboratory. Green tea dose was based on the study by Panza et al.[15] Participants received green tea capsules containing 2 g of concentrated powder – approximately 1,960 mg in polyphenols (636 mg of epigallocatechin gallate) and 20 mg of caffeine – or placebo containing 2 g of cornstarch powder, both swallowed with water. The capsules were administered to patients after blood sample collection. Thirty minutes later, exercise sessions were initiated.

Regular consumption of green tea, polyphenols, catechins and caffeine, as well as consumption of these products on the previous day were assessed 24-hour recall as proposed by Fisberg et al.[16] The instrument was applied on three non-consecutive days to evaluate dietary intake on two weekdays and one weekend day.

During a 48-hour washout period, prior to the sessions, all participants were instructed to refrain from foods rich in polyphenols and epigallocatechin – dark chocolate, red wine, black and green tea, grapes, and apples. Data were analyzed using the Nutwin software (version 1.5, 2003, Brazil). Hypertensive patients were asked to maintain their eating habits during the study period.

Blood pressure measurement

BP was measured in triplicate at intervals of one minute between measurements in the arm with the highest reading. Individuals had their BPs checked before (at rest), immediately after, and during the 60-minute period post-exercise. BP at rest was verified after the subjects remained seated for 10 minutes; right after the treadmill walking session, BP was checked in seated position and, during the 60-minute recovery period, measurements were taken every 10 minutes. All measurements were performed according to the Brazilian Society of Cardiology and the Brazilian Society of Hypertension guidelines.[17]

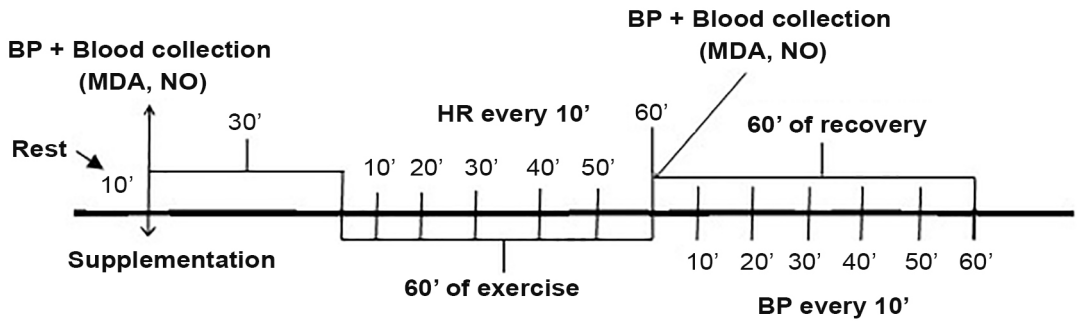

Figure 1 – *Experimental design diagram.*
BP: blood pressure; MDA: malondialdehyde; NO: nitrite; HR: heart rate.

Blood collection and laboratory analysis

Samples of 10 mL of blood were collected from the antecubital vein before and after the exercise, of which 5 mL was placed in test tubes containing EDTA, and carefully homogenized by repeated inversion, and 5 mL was placed in tubes without anticoagulant. The samples were then centrifuged at 3,000 rpm for 20 minutes. Plasma was transferred to microtubes and refrigerated until analysis.

Oxidative activity was quantified by the thiobarbituric acid reaction with products from hydroperoxides decomposition. A volume of 250 μL of sample was homogeneized with KCl and incubated at 37° C in a water bath for 60 minutes. The mixture was then precipitated with 35% perchloric acid and centrifuged at 14,000 rpm for 10 minutes at 4° C. The supernatant was transferred to new tubes to which 400 μl of 0.6% thiobarbituric acid was added, and the mixture incubated at 95-100° C for 30 min. After cooling, the material was read by a spectrophotometer at wavelength of 532 nm. NO measurement was based on the Griess method. Reagent was prepared utilizing equal parts of 5% phosphoric acid, 0.1% N-1-naphthalenediamine (NEED), 1% sulphanilamide, 5% in phosphoric acid and distilled water. To accomplish the test, 100 μL of 10% homogenate supernatant made with potassium phosphate buffer was added to 100 μL of Griess reagent. Regarding the control, 100 μL of the reagent was added to 100 μL of buffer and series of dilutions were prepared to construct the standard curve (100, 50, 25, 12.5, 6.25, 3.12, 1.56 μm) of NO concentration. The test was performed in a 96 well-plate template and absorbance was read at 560 nm.[18]

Data analysis

The Shapiro-Wilk and Levene tests were used to test the normality and variability of data, respectively. One-way ANOVA test was applied to compare baseline data between the procedures, and repeated measures ANOVA was used for analysis of heart rate and blood pressure measurements. Data are expressed in mean and standard deviation. Statistical significance was set at 0.05. Analyses were performed using the Instat software (GraphPAdInstat, San Diego, CA, USA) version 3.0.

Results

Subjects had normal glucose and cholesterol levels, and controlled BP despite being diagnosed with hypertension. Before the two experimental procedures, participants had similar values of HR and BP at rest, as well as plasma MDA and NO levels (Table 1). Analyses of the 24-hour recall questionnaires revealed an average consumption of 298 ± 67 mg of antioxidants and 135 ± 49 mg of caffeine.

There was no statistical difference in HR at any time between both procedures as shown in Figure 2, and the intensity of exercise was similar in both occasions. Ratings of perceived exertion reported by the subjects were 11-14 on Borg scale. However, participants exercised at an intensity that was lower than that requested by the investigators. On the GTE day, the minimum mean intensity reached by hypertensive patients was 27.8 ± 12.6% of the HRmax at 10 minutes, whereas the maximum was 52.3 ± 12.2% at 60 minutes, with a mean between the minimum and the maximum of 39.8 ± 8.7% of the HRmax. On PLE day, the minimum mean intensity was 29.2 ± 14.1%

at 10 minutes and the maximum was 50.2 ± 18.9% at 60 minutes, with an average of 38.0 ± 7.0% of the HRmax.

BP response to exercise can be seen in Figure 3. On PLE day, there was a significant decrease in post-exercise systolic BP as compared with the rest period. On the other hand, in the GTE procedure, significant PEH occurred only at 20 and 40 minutes post exercise ($p = 0.02$ and $p = 0.03$, respectively). The magnitude of PEH was statistically higher on PLE day at 10 to 30 minutes as compared with those on GTE ($p = 0.03$ for both), indicating a significant PEH inhibition promoted by the ingestion of green tea.

Diastolic PEH occurred only on PLE day, and was significant at 20 minutes of recovery ($p = 0.04$). The ingestion of green tea caused a post-exercise hypertensive response, unlike the PLE experiment. (Figure 3). However, no statistical differences were found between diastolic values post-PLE and post-GTE.

The effects of MDA and NO are presented in Figure 4. There was a subtle, but not relevant reduction in MDA values between pre- and post-exercise conditions in both procedures. Similarly, no changes were observed in NO concentration in response to exercise or to green tea ingestion.

Table 1 – Baseline anthropometric, hemodynamic and biochemical data of participants

Variable	GTE	PLE	p values
HRR (bpm)	79.2 ± 10.8	75.5 ± 4.6	0.23
SBPR (mm/Hg)	117.6 ± 10.0	118.1 ± 12.6	0.90
DBPR (mm/Hg)	79.3 ± 7.8	79.2 ± 8.4	0.97
BMI (kg/m^2)		28.7 ± 7.6	
Glicose (mg/dl)		96.6 ± 20.6	
Total cholesterol (mg/dl)		171.1 ± 43.9	
HDL (mg/dl)		44.3 ± 16.0	
Triglycerides (mg/dl)		191.8 ± 73.6	
Malondialdehyde (μM)		5.8 ± 1.0	
Nitrite (μM)		67.7 ± 43.5	

HRR: heart rate at rest; SBPR: systolic blood pressure at rest; DBPR: diastolic blood pressure at rest; BMI: body mass index; GTE: green tea + exercise; PLE: placebo + exercise; HDL: high density lipoprotein. Data as mean and standard deviation.

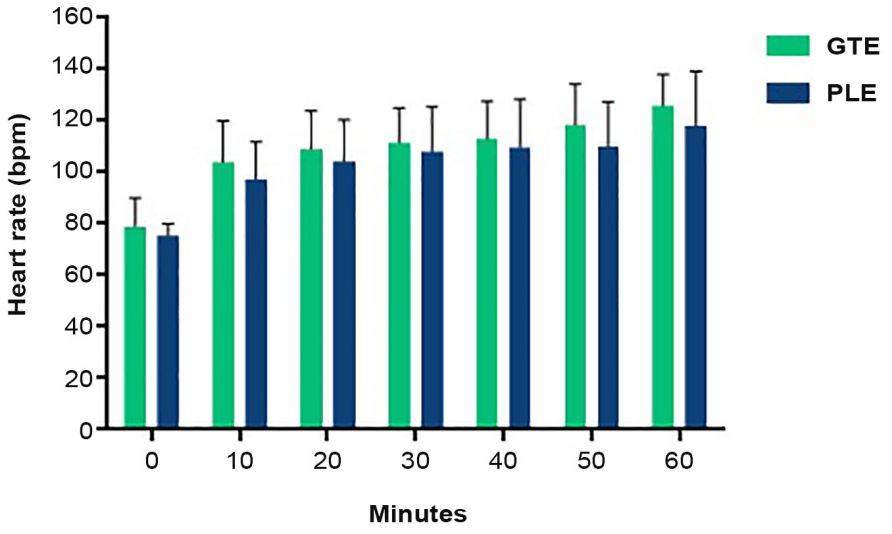

Figure 2 – *Heart rate response to exercise and green tea or placebo intake.*
Data as mean and standard deviation. No statistically significant difference was observed between procedures ($p > 0.05$). GTE: green tea + exercise; PLE: placebo + exercise.

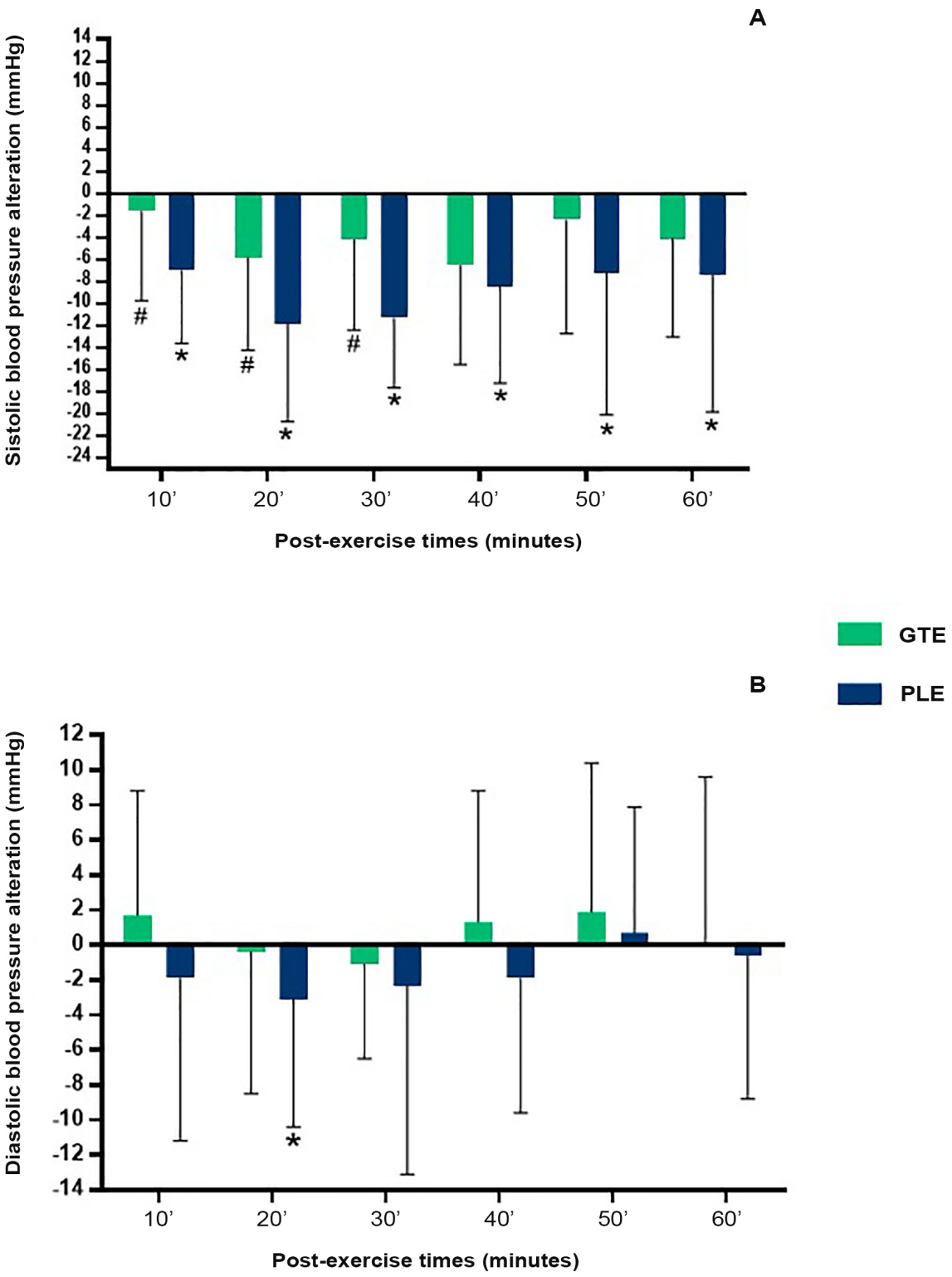

Figure 3 – *Absolute variation in blood pressure post-exercise compared with systolic (panel A) and diastolic components (panel B) at rest. Data as mean and standard deviation. GTE: green tea + exercise; PLE: placebo + exercise. *statistically significant PEH ($p < 0.05$). # $p < 0.05$ compared with placebo.*

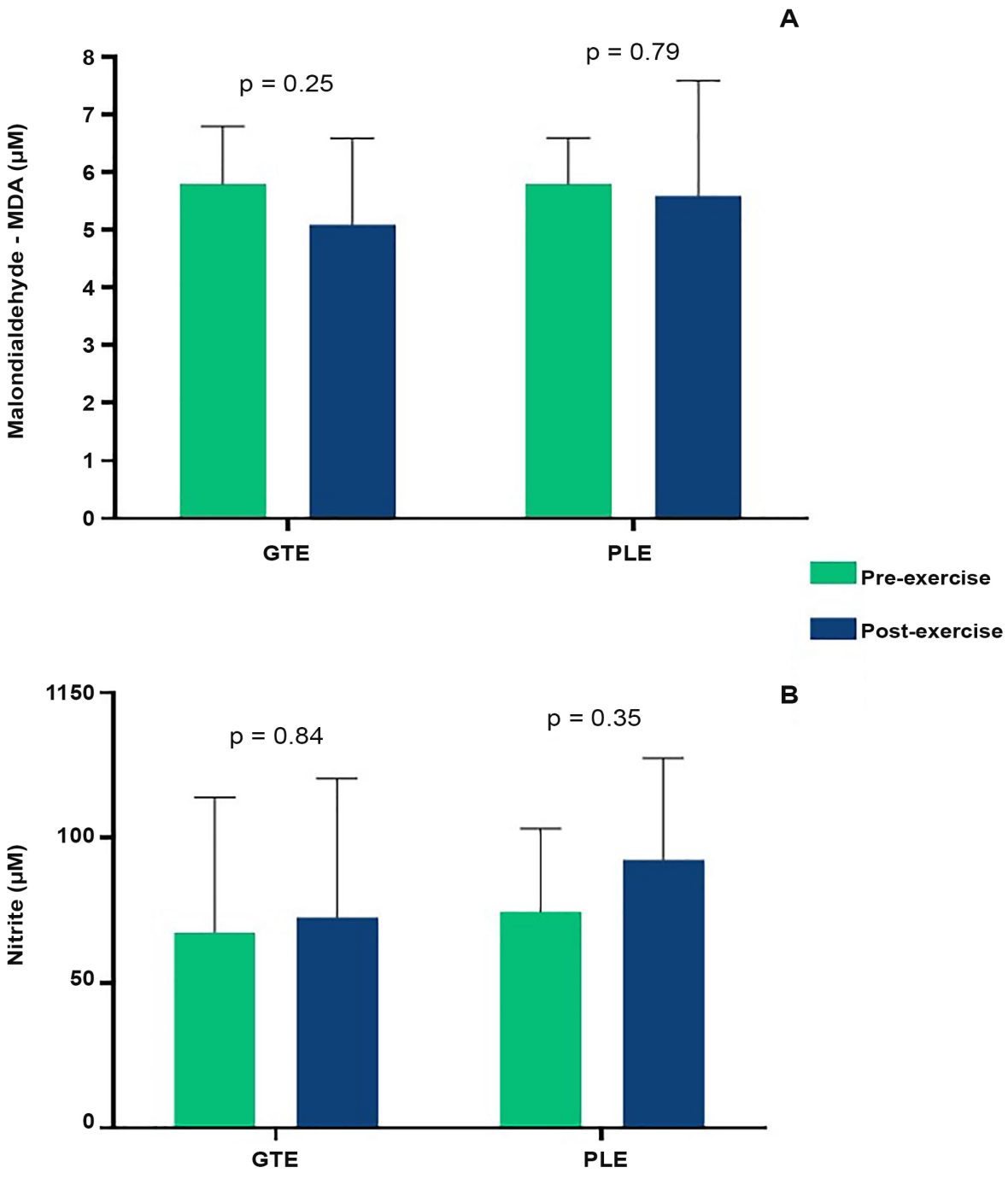

Figure 4 – *Plasma malondialdehyde (panel A) and nitrite (panel B) before and after exercise session. Data as mean and standard deviation. GTE: green tea + exercise; PLE: placebo + exercise. There was no statistically significant difference between pre and post-exercise in all moments (p > 0.05).*

Discussion

Data presented in this study showed that the ingestion of green tea significantly inhibited systolic hypotension and promoted a subtle hypertensive diastolic response after a session of aerobic exercise in middle-aged hypertensive patients.

Previous studies of Bogdanski et al.[19] and Mozaffari-Khosravi et al.[20] showed that treatment with 379 mg of green tea for three months and 3 g for four months, respectively, resulted in decreased BP in hypertensive adults. This benefits of green tea are attributed to its high content of antioxidants and anti-inflammatory catechins.[15,19,21] Nonetheless, this data may not reflect the effects of a single dose of green tea administration neither in BP nor in antioxidant activity in response to a session of physical exercise. Belza et al.[22] found that a single dose of green tea (500 mg) did not cause significant effects on the blood pressure response of young adults. The study, however, did not include physical exercise in its protocol.

In addition, a single dose of green tea would not be enough to promote an antioxidant activity that could potentiate the PEH. On the other hand, it is known that the vasoconstrictor effects of caffeine occur soon after intestinal absorption, reaching its maximal bloodstream concentration in 15 to 120 minutes after ingestion.[23] This is reinforced by previous studies showing that intravenous,[24] oral[4] administration of caffeine and even coffee intake[5] promoted a hypertensive response after sessions of aerobic exercises. Therefore, in spite of the various substances present in green tea, we may suggest that caffeine contained in green tea was responsible for the attenuating effect on PEH and the hypertensive diastolic response observed in this study.

As far as we know, this was the first study to investigate the effects of green tea ingestion on post-exercise BP response. Arazi et al.[25] supplemented hypertensive women for three weeks prior to the intervention with resistance exercise. The authors showed no changes in PEH, except in mean arterial pressure immediately and 15 minutes after the exercise session. Comparisons between these results with ours are inadequate because these authors worked with chronic supplementation and resistance exercise, while we investigated a single dose of green tea and aerobic exercise.

Practical implication of these findings is that it is common for people to use green tea in their diets. This type of tea is one of the most popular drinks in the world.[26] Thus, hypertensive consumers must be instructed to avoid the ingestion of green tea prior, during or after exercise sessions. However, since this is the first study to demonstrate that green tea ingestion affects BP response to exercise, it is prudent that further studies be undertaken to confirm the presence of other influential factors, as well as green tea dose-dependent effects and duration of the effects.

The following aspects should be considered in future studies: first, it is still necessary to know how long before or after exercise the ingestion of green tea could affect the PEH. Our results suggest a 30 minute-period before exercise. Second, our study did not determine the duration of green tea effects on post-exercise BP. To clarify this point, further studies should include a longer BP monitoring period after exercise than that we used in the present study (60 minutes). Third, other dosages of green tea should be tested, to analyze whether doses lower than 2 g (used in this study) would prevent the post-exercise hypertensive phenomenon. Finally, since the subjects of this study were not regular users of green tea prior to the study, we cannot affirm that attenuation in PEH in response to 2 g of green tea intake would also be observed in regular consumers.

Conclusion

Data obtained from this study showed that 2 g of green tea supplementation prior to a session of aerobic exercises decreases the magnitude of post-exercise systolic hypotension and promotes a diastolic hypertensive response after exercise in middle-aged hypertensive patients.

Acknowledgements

We thank the Committee of Postgraduate Studies of the Federal University of Paraiba.

Author contributions

Conception and design of the research: Silva AS. Acquisition of data: Miranda Neto M, Silva TF, Lima FF. Analysis and interpretation of the data: Miranda Neto M, Silva RSB, Silva TF, Lima FF, Silva AS. Statistical analysis: Miranda Neto M, Silva TF, Lima FF, Silva AS. Obtaining financing: Silva TF, Silva AS. Writing of the manuscript: Miranda Neto M, Silva RSB, Silva TF, Lima FF, Silva AS. Critical revision of the manuscript for intellectual content: Miranda Neto M, Silva RSB, Silva TF, Lima FF, Silva AS.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by Pró-reitoria de Pós-graduação e Pesquisa – PRPG, Universidade Federal da Paraíba.

Study Association

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

References

1. Laterza MC, Rondon MU, Negrão CE. The anti-hypertensive effects of exercise. Rev Bras Hipertens. 2007;14(2):104-11.
2. Casonatto J, Polito MD. Post-exercise hypotension: a systematic review. Rev Bras Med Esporte. 2009;15(2):151-7.
3. Santana HA, Moreira SR, Neto WB, Silva CB, Sales MM, Oliveira VN, et al. The higher exercise intensity and the presence of allele I of ACE gene elicit a higher post-exercise blood pressure reduction and nitric oxide release in elderly women: an experimental study. BMC Cardiovasc Disord. 2011;11:71.
4. Cazé RF, Franco GA, Porpino SK, De Souza AA, Padilhas OP, Silva AS. Caffeine influence on blood pressure response to aerobic exercise in hypertensive subjects. Rev Bras Med Esporte. 2010;16(5):324-8.
5. Souza AA, Silva RS, Silva TF, Tavares RL, Silva AS. Influence of different doses of coffee on post-exercise blood pressure response. Am J Cardiovas Dis. 2016;6(4):145-52.
6. Fukino Y, Ikeda A, Maruyama K, Aoki N, Okubo T, Iso H. Randomized controlled trial for an effect of green tea-extract powder supplementation on glucose anormalities. Eur J Clin Nutr. 2008; 62(8):953-60.
7. Nantz MP, Rowe CA, Bukowski JF, Percival SS. Standardized capsule of Camellia sinensis lowers cardiovascular risk factors in a randomized, double-blind, placebo-controlled study. Nutrition. 2009;25(2):147-54.
8. Yang CS, Hong J, Hou Z, Sang S. Green tea polyphenols: antioxidative and prooxidative effects. J Nutr. 2004;134(11):3181S.
9. Khalesi S, Sun J, Buys N, Jamshidi A, Nikbakht-Nasrabadi E, Khosravi-Boroujeni H. Green tea catechins and bloos pressure: a systematic review and meta-analysis of randomised controlled trials. Eur J Nutr. 2014; 53(6): 1299-311.
10. Nóbrega TK, Moura Júnior JS, Brito AF, Gonçalves MC, Martins CO, Silva AS. Walking/running or a recreative soccer game presents similar effectiveness in inducing post-exercise hypotension. Rev Bras Med Esporte. 2013;19(1):31-4.
11. Brito Ade F, de Oliveira CV, Brasileiro-Santos Mdo S, Santos Ada C. Resistance exercise with different volumes: blood pressure response and forearm blood flow in the hypertensive elderly. Clin Interv Aging. 2014;9:2151-8.
12. Loiola Souto A, Moreira Lima L, Aparecida Castro E, Peixoto Veras R, Segheto W, Camargos Zanatta T, et al. Blood pressure in hypertensive women after aerobics and hydrogymnastics sessions. Nutr Hosp. 2015;32(2):823-8.
13. Karvonen MJ, Kentala E, Mustala O. The effects of training on heart rate; a longitudinal study. Ann Med Exp Biol Fenn. 1957;35(3):307-15.
14. Borg GA, Noble BJ. Perceived exertion. Exerc Sport Sci Rev. 1974;2:131-54.
15. Panza VS, Waslawik E, Ricardo Schütz G, Comin L, Hetch KC, da Silva EL. Consumption of green tea favorably affects oxidative stress markers in weight-trained men. Nutrition. 2008;24(5):433-42.
16. Fisberg RM, Slater B, Marchioni DM, Martini LA. Inquéritos alimentares: métodos e bases científicas. Barueri (SP): Manole; 2005.
17. Sociedade Brasileira de Cardiologia; Sociedade Brasileira de Hipertensão; Sociedade Brasileira de Nefrologia. [VI Brazilian Guidelines on Hypertension]. Arq Bras Cardiol. 2010;95(1 Suppl):1-51. Erratum in: Arq Bras Cardiol. 2010;95(4):553.
18. Green LC, Ruiz de Luzuriaga K, Wagner DA, Rand W, Istfan N, Young VR, et al. Nitrate biosynthesis in man. Proc Natl Acad Sci USA. 1981;78(12):7764-8.
19. Bogdanski P, Suliburska J, Szulinska M, Stepien M, Pupek-Musialik D, Jablecka A. Green tea extract reduces blood pressure, inflammatory biomarkers, and oxidative stress and improves parameters associated with insulin resistance in obese, hypertensive patients. Nutr Res. 2012;32(6):421-7.
20. Mozzaffari-Khosravi H, Ahadi Z, Barzegar K. The effect of green tea and sour tea on blood pressure of patients with type 2 diabetes: a randomized clinical trial. J Diet Suppl. 2013;10(2):105-15.
21. Klaunig JE, Xu Y, Han C, Kamendulis LM, Chen J, Heiser C, et al. The effect of tea consumption on oxidative stress in smokers and nonsmokers. Proc Soc Exp Biol Med. 1999;220(4):249-54.
22. Belza A, Toubro S, Astrup A. The effect of caffeine, green tea and tyrosine on thermogenesis and energy intake. Eur J Clin Nutr. 2009;63(1):57-64.
23. Sinclair CJ, Geiger JD. Caffeine use in sport: a pharmacological review. J Sports Med Phys Fitness. 2000;40(1):71-9.
24. Notarius CF, Morris BL, Floras JS. Caffeine attenuates early post-exercise hypotension in middle-age subjects. Am J Hypertens. 2006;19(2):184-8.
25. Arazi H, Samami N, Kheirkhah J, Taati B. The effect of three weeks green tea extract consumption on blood pressure, heart rate responses to a single bout resistance exercise in hypertensive women. High Blood Press Cardiovasc Prev. 2014;21(3):213-9.
26. Suzuki T, Pervin M, Goto S, Isemura M, Nakamura Y. Beneficial effects of tea and the green tea catechin epigallocatechin-3-gallate on obesity. Molecules. 2016;21(10):pii.E1305.

ORIGINAL ARTICLE

Study of Dabigatran Use in a Brazilian Public Hospital Specialized in Cardiology

Luise Barros Martins,[1] Ivis Levy Fernandes Martins,[1] Raíssa Miranda Silva,[1] Flávia Valéria dos Santos Almeida,[1, 2] Christianne Bretas Vieira Scaramello[1]

Universidade Federal Fluminense, Niterói, Rio de Janeiro;[1] Instituto Nacional de Cardiologia, Rio de Janeiro,[2] RJ – Brazil

Abstract

Background: During its commercialization phase, unprecedented effects of new medicaments can be discovered. Dabigatran is an anticoagulant approved by Brazilian National Health Surveillance Agency in 2008.

Objectives: To assess safety, effectiveness adverse event profile and adherence to dabigatran (110 mg and 150 mg) prescribed for patients with non-valvular atrial fibrillation.

Methods: Patients taking dabigatran were subjected to interviews during the first year of treatment, evaluating the prescription depending on the dose, age, gender and risk factors as well as the prevalence of adverse events and the profile of the patients involved.

Results: Between the beginning and the end of the study there was a reduction in the number of subjects using this anticoagulant (10% for the dose of 110 mg and 30% for the dose of 150 mg), without changes in the proportions of individuals regarding to gender (men ≅65%), age (age <75 anos ≅80%), anticoagulation previous history (≅85%) and risk scores for thromboembolic (CHA2DS2 ≥ VASc = 2 ≅80%) and bleeding (HASBLED <3 ≅50% dose 110 mg and ≅85% dose 150 mg) events. The most common adverse event was dyspepsia (≥10%), regardless of gender, but less frequently in patients over 75 years of age (≅20% of cases). Dyspepsia related to dabigatran was mainly associated to its combination with beta-blockers (≅70%), but minoritarily with oral hypoglycemic (≅20%), antiplatelet agents (≅10%), proton pump inhibitors (≅30%) and antagonists H2 (≅3%). Therapeutic adherence was ≅60% regardless of the described adverse events. There were no cases of thromboembolic event and major bleeding.

Conclusions: Dabigatran has shown to be safe and effective in the evaluated conditions. (Int J Cardiovasc Sci. 2017;30(4):334-342)

Keywords: Pharmacovigilance; Anticoagulants; Thrombin; Atrial fibrillation.

Introduction

Atrial fibrillation is a supraventricular arrhythmia associated to several complications, such as systemic thromboembolism, which is responsible for the morbidity and mortality of patients with this arrhythmia. Therefore, treatment includes the use anticoagulants.[1-3]

Dabigatran etexilate, a prodrug, is quickly converted into dabigatran, an anticoagulant that directly and reversibly inhibits thrombin, impeding the conversion of fibrinogen into fibrin.[4-6] Doses of 110 mg and 150 mg of dabigatran etexilate, to prevent stroke in patients with atrial fibrillation, were approved by the FDA in 2010, and by the EMA and ANVISA in 2011.[7,8]

The development of new medication involves the synthesis of molecules with therapeutic potential that are submitted to pre-clinical tests in animals, and then to clinical studies in humans.[9-11] These are divided into four stages, the last of which encompasses post-marketing surveillance to map: adverse and rare effects or those which can only be observed in the long run;

Mailing Address: Christianne B. V. Scaramello
Rua Professor Hernani Mello, 101. Postal Code: 24210-130, Ingá, Niterói, RJ – Brazil
E-mail: chrisbretas@gmail.com; christiannebretas@vm.uff.br

DOI: 10.5935/2359-4802.20170052

Manuscript received July 13, 2016; revised manuscript August 01, 2016; accepted April 17, 2017.

adherence to the treatment; and drug interaction.[12] In Brazil, dabigatran etexilate is not distributed by the Unified Health System (SUS), nor is it standardized in many hospitals, which hinders the monitoring of its use. Thus, the objective of the present study includes the assessment of safety, effectiveness, and adherence to dabigatran prescribed to non-valvular atrial fibrillation in a public Brazilian hospital, specialized in cardiology, by characterizing the profile of adverse events.

Methods

This pharmacovigilance study was observational, analytical, longitudinal and prospective, to evaluate effectiveness and safety and characterize adverse events associated to a 12-month use of 110 and 150 mg doses of dabigatran in outpatients with non-valvar atrial fibrillation. The drug was obtained with resources from the hospital where the study was developed upon a bidding process and after its insertion on the list of medications standardized by the Institution's Pharmacy and Therapeutics Commission.

The study started with 139 patients, of which 33 received 110 mg. Exclusion criteria included: pregnancy, age < 18 years, and the presence of a heart valve prosthesis. Data collection was done between January 2013 and December 2014 (CAAE 03455512.5.0000.5272). All participants, or legal guardians, signed a free consent form.

Monthly interviews were done, and data were analysed by trimester for the following factors: patients' age and gender, risk scores for bleeding events (HASBLED) and thromboembolic events (CHA_2DS_2-VASc), therapeutic associations, and adverse reactions observed after the beginning of the new anticoagulant pharmacotherapy.

Estimation on patient adherence to the use of dabigatran was done through the method of recording drug removal described by Obreli-Neto et al. (2011),[13] and patients considered as having adhered were those with an agreement level of 80 to 115%.

The study had a few limitations:

- Relatively short follow-up time, small sample for analysis and monitoring of patients in only one health unit;
- Deaths, suspensions, and withdrawals from the treatment;
- Lack of accessibility to data on events that took place outside the health unit since it does not have emergency care.

Statistical analysis

The descriptive statistical analysis was done through SPSS 22.0, with determination of absolute and relative frequency for categorical variables, thus determining a confidence interval of 95% and relative variation.

Results

Table 1 compares the profile of patients who joined the study to those who remained in it for at least one year of treatment with dabigatran. Most patients were under 75 years of age, and, in the case of the higher dose, most of them were male. Regarding risk scores, both the higher and the lower doses of dabigatran were prescribed especially to patients with a high risk of thromboembolic events, which was assessed by the score CHA_2DS_2-VASc. By analysing HASBLED, it was possible to see that the 150 mg dose was prescribed especially to patients at a low risk for bleeding. On the other hand, the frequency of 110 mg prescriptions was similar among patients with high and low risk of bleeding. By comparing the profiles of patients at the beginning and at the end of the study, we can observe that there was no variation of proportions. We can, however, see a reduction of approximately 30% of the number of individuals on anticoagulants in the 150 mg dose group, while that reduction is only of 10% in the 110 mg dose.

Analysis of the data about prescription frequency of 110 mg and 150 mg doses for patients over 75 years of age (Table 1) at the end of the study shows that the lower dose was prioritized for older patients (Relative variation = 0.31; CI – 0.11 – 0.91).

The most frequently reported adverse events during the monthly dispensing of dabigatran are shown in Table 2. It is noteworthy that, in general, dyspepsia was the highest occurrence, with a mean frequency above 10%, followed by minor bleeding. Additionally, we can observe a reduction of adverse events and of the number of patients who remained in the study with each trimester. However, specifically in the third trimester, the number of individuals on the 110 mg dose increased, while the use of the higher dose went down. In the fourth trimester, the number of patients on the 110 mg dose was maintained, while the number of those on the higher dose decreased again.

Table 1 – Comparison between the profiles of patients who entered the study and those who remained for the 1st year of treatment with dabigatran 110 and 150 mg

	Dabigatran 110 mg			Dabigatran 150 mg		
	Beginning of the study (N = 33)	End of the study (N = 30)	Relative variation (CI) Beginning x End	Beginning of the study (N = 106)	End of the study (N = 68)	Relative variation (CI) Beginning x End
Age Group						
< 75 years (%; N)	75.8% (25)	76.7% (23)	1.01 (0.77-1.33)	87.7% (93)	92.6% (63)	1.05 (0.96-1.16)
≥75 years (%; N)	24.2% (8)	23.3% (7)	0.96 (0.40-2.33)	12.3% (13)	7.3% (5)	0.60 (0.22-1.61)
Relative variation (CI) Age Group	0.32 (0.17-0.60)	0.30 (0.15-0.60)	–	0.14 (0.08-0.23)	0.08 (0.03-0.18)	–
Gender						
Female (%; N)	42.4% (14)	36.7% (11)	0.86 (0.47-1.6)	34% (36)	29.4% (20)	0.87 (0.55-1.36)
Male (%; N)	57.6% (19)	63.3% (19)	1.10 (0.74-1.64)	66% (70)	70.6% (48)	1.07 (0.87-1.31)
Relative variation (CI) Gender	1.36 (0.83-2.22)	1.73 (1.00-2.97)	–	1.94 (1.44-2.62)	2.40 (1.61-3.60)	–
CHA_2DS_2-VASc score						
0 – 1 (%; N)	12.1% (4)	16.7% (5)	1.38 (0.41-4.65)	21.7% (23)	26.5% (18)	1.22 (0.71-2.08)
≥ 2 (%; N)	87.9% (29)	83.3% (25)	0.95 (0.77-1.16)	78.3% (83)	73.5% (50)	0.94 (0.79-1.12)
Relative variation (CI) CHA_2DS_2-VASc	7.25 (2.89-18.33)	5.00 (2.21-11.31)	–	3.61 (2.48-5.25)	2.78 (1.82-4.23)	–
HASBLED score						
0 – 2 (%; N)	48.5% (16)	56.7% (17)	1.17 (0.73-1.87)	86.8% (92)	85.3% (58)	0.98 (0.87-1.11)
≥ 3 (%; N)	51.5% (17)	43.3% (13)	0.84 (0.50-1.42)	13.2% (14)	14.7% (10)	1.11 (0.52-2.36)
Relative variation (CI) HASBLED	1.06 (0.65-1.72)	0.76 (0.46-1.28)	–	0.15 (0.09-0.25)	0.17 (0.10-0.31)	–

CI: confidence interval.

Table 3 shows the profile of patients who reported dyspepsia. In general, most individuals were under 75 years of age and presented high risk for thromboembolic events and low risk for bleeding events. No difference was found between genders.

There was a positive correlation between the use of beta-blockers and the occurrence of dyspepsia, as well as an inversely proportional relation between the occurrence of this adverse event and dabigatran association to proton pump inhibitors, histamine H2-receptor antagonists, oral hypoglycemic agents, and antiplatelets (Table 4). The other reported therapeutic combinations did not influence the occurrence of this adverse event (data not shown).

Throughout the four trimesters, most patients adhered to the treatment (Table 5). The occurrence of dyspepsia and minor bleeding did not differ between those who adhered and those who did not. The percentage of individuals that adhered to the treatment was higher among those on dabigatran 110 mg, while in the fourth trimester, the percentage of adherence was higher among those on 150 mg.

No cases of major bleeding or thromboembolic event were recorded during the study.

Discussion

Although the profile of patients at the end of the treatment is similar to that of the beginning, we found a reduction in the total number of individuals on the medication due to treatment suspension or termination and deaths. Such reduction occurred mainly in the higher

Table 2 – Adverse events reported in each of the treatment's four trimesters

Adverse events	1º trimester		2º trimester		3º trimester		4º trimester	
	110 mg N=33	150 mg N=106	110 mg N=27	150 mg N=80	110 mg N=30	150 mg N=71	110 mg N=30	150 mg N=68
Dyspepsia								
% (N)	36.4 % (12)	44.3 % (47)	3.7% (1)	12.5 % (10)	0.0% (0)	16.9% (12)	10.0% (3)	10.3% (7)
IC	22.2-53.4	35.2-53.8	0.7-18.3	6.9-21.5	0.0-11.3	9.9-27.3	3.5-25.6	5.1-19.8
Vomiting								
% (N)	3.0% (1)	4.7% (5)	0.0% (0)	0.0% (0)	0.0% (0)	1.4% (1)	0.0% (0)	0.0% (0)
IC	0.5-15.3	2.0-10.6	0.0-12.5	0.0- 4.6	0.0-11.3	0.2- 7.6	0.0-11.3	0.0-5.3
Dyspnea								
% (N)	12.1 % (4)	4.7% (5)	7.4% (2)	6.2% (5)	10.0% (3)	1.4% (1)	10.0% (3)	1.5% (1)
IC	4.8-27.3	2.0-10.6	2.1-23.4	2.7-13.8	3.5-25.6	0.2- 7.6	3.5-25.6	0.3-7.9
Bleeding								
% (N)	15.1 % (5)	11.3 % (12)	3.7% (1)	10.0% (8)	6.7% (2)	9.9% (7)	13.3% (4)	5.9% (4)
IC	6.6-30.9	6.6-18.7	0.7-18.28	5.1-18.5	1.8-21.3	4.9-19.0	5.3-29.7	2.3-14.2
Edema								
% (N)	3.0 % (1)	1.9% (2)	0.0% (0)	2.5% (2)	3.3% (1)	2.8% (2)	10.0% (3)	2.9% (2)
IC	0.5-15.3	0.5- 6.6	0.0-12.5	0.7- 8.7	0.6-16.7	0.8- 9.7	3.5-25.6	0.8-10.1
Fatigue								
% (N)	6.1% (2)	6.6 % (7)	14.8% (4)	7.5% (6)	10.0% (3)	5.6% (4)	10.0% (3)	2.9% (2)
IC	1.7-19.6	3.2-13.0	5.9-32.5	3.5-15.4	3.5-25.6	2.2-13.6	3.5-25.6	0.8-10.1

CI: confidence interval.

Table 3 – Characterization of patients who presented dyspepsia associated to dabigatran use in each of the four trimesters of follow-up

Dyspepsia	1º Trimester		2º Trimester		3º Trimester		4º Trimester	
	110 mg (N = 12)	150 mg (N = 47)	110 mg (N = 1)	150 mg (N = 10)	110 mg (N = 0)	150 mg (N = 12)	110 mg (N = 2)	150 mg (N = 8)
Age Group								
< 75 years % (N)	83.3% (10)	82.9%(39)	100%(1)	90.0%(9)	0.0%(0)	100%(12)	100%(2)	75.0%(6)
≥75 years % (N)	16.7%(2)	17.1%(8)	0.0% (0)	10.0%(1)	0.0% (0)	0.0% (0)	0.0% (0)	25.0%(2)
Relative variation (CI)	0.20 (0.06-0.73)	0.20 (0.11-0.39)	ND	0.11 (0.17-0.72)	ND	ND	ND	0.33 (0.09-1.18)
Gender								
Female% (N)	58.3%(7)	42.5%(20)	100%(1)	10.0%(1)	0.0% (0)	33.3%(4)	0.0% (0)	50.0%(4)
Male% (N)	41.6%(5)	57.4%(27)	0.0% (0)	90.0%(9)	0.0% (0)	66.7%(8)	100%(2)	50.0%(4)
Relative variation (CI)	0.71 (0.32-1.63)	1.35 (0.89-2.04)	ND	9.00 (1.38-58.44)	ND	2.00 (0.82-4.89)	ND	1.00 (0.37-2.66)
CHA_2DS_2-VASc score								
0 – 1% (N)	8.3%(1)	17.1%(8)	0.0% (0)	20.0%(2)	0.0% (0)	33.3%(4)	0.0% (0)	12.5%(1)
≥ 2% (N)	91.7%(11)	82.9%(39)	100%(1)	80.0%(8)	0.0% (0)	66.7%(8)	100%(2)	87.5%(7)
Relative variation (CI)	11.00 (1.67-72.40)	4.87 (2.56-9.30)	ND	4.00 (1.11-14.35)	ND	2.00 (0.82-4.89)	ND	7.00 (1.10-44.60)
HASBLED score								
0 – 2% (N)	50.0%(6)	89.4%(42)	100%(1)	90.0%(9)	0.0% (0)	100%(12)	100%(2)	100%(8)
≥ 3% (N)	50.0%(6)	10.6%(5)	0.0% (0)	10.0%(1)	0.0% (0)	0.0% (0)	0.0% (0)	0.0% (0)
Relative variation (CI)	1.00 (0.45-2.23)	0.12 (0.05-0.27)	ND	0.11 (0.02-0.72)	ND	ND	ND	ND

CI: confidence interval; ND: not determinable.

Table 4 – Therapeutic associations to dabigatran in patients who presented dyspepsia in each of the four trimesters of follow-up

Dyspepsia	1º Trimester		2º Trimester		3º Trimester		4º Trimester	
	110 mg (N = 12)	150 mg (N = 47)	110 mg (N = 0)	150 mg (N = 12)	110 mg (N = 0)	150 mg (N = 12)	110 mg (N = 2)	150 mg (N = 8)
Hypoglycemic agent								
Yes% (N)	16.7%(2)	23.4%(11)	0.0%(0)	16.7%(2)	0.0%(0)	16.7%(2)	50.0%(1)	12.5%(1)
No% (N)	83.3% (10)	76.6% (36)	0.0%(0)	83.3%(10)	0.0%(0)	83.3%(10)	50.0% (1)	87.5%(7)
Relative variation (CI)	5.00 (1.38-18.17)	3.27 (1.90-5.62)	ND	5.00 (1.38-18.17)	ND	5.00 (1.38-18.17)	1.00 (0.14-7.10)	7.00 (1.10-44.61)
Antiplatelet agent								
Yes% (N)	8.3%(1)	10.6%(5)	0.0%(0)	40.0%(4)	0.0%(0)	8.3%(1)	0.0%(0)	12.5%(1)
No% (N)	91.7%(11)	89.4%(42)	100%(1)	60.0%(6)	0.0%(0)	91.7%(11)	100%(2)	87.5%(7)
Relative variation (CI)	11.00 (1.67-72.40)	8.40 (3.65-19.35)	ND	1.50 (0.60-3.73)	ND	11.00 (1.67-72.40)	ND	7.00 (1.10-44.61)
Beta-blocker								
Yes% (N)	75.0%(9)	59.6%(28)	100%(1)	80.0%(8)	0.0%(0)	91.7%(11)	100%(2)	62.5%(5)
No% (N)	25.0%(3)	40.4%(19)	0.0%(0)	20.0%(2)	0.0%(0)	8.3%(1)	0.0%(0)	37.5%(3)
Relative variation (CI)	0.33 (0.12-0.94)	0.68 (0.45-1.03)	ND	0,25 (0.07-0.90)	ND	0.09 (0.01-0.60)	ND	0.60 (0.21-1.70)
PPI								
Yes% (N)	8.3%(1)	23.4%(11)	100%(1)	40.0%(4)	0.0%(0)	16.7%(2)	50.0%(1)	12.5%(1)
No% (N)	91.7%(11)	76.6%(36)	0.0%(0)	60.0%(6)	0.0%(0)	83.3%(10)	50.0%(1)	87.5%(7)
Relative variation (CI)	11.00 (1.67-72.40)	3.27 (1.90-5.62)	ND	1.50 (0.60-3.73)	ND	5.00 (1.38-18.17)	1.00 (0.14-7.10)	7.00 (1.10-44.61)
Antagonist H2								
Yes% (N)	0.0%(0)	4.2%(2)	0.0%(0)	10.0%(1)	0.0%(0)	8.3%(1)	0.0%(0)	0.0%(0)
No% (N)	100%(12)	95.8%(45)	0.0%(0)	90.0%(9)	0.0%(0)	91.7%(11)	100%(2)	100%(8)
Relative variation (CI)	ND	22.5 (5.79-87.44)	ND	9.00 (1.39-58.44)	ND	11.00 (1.67-72.40)	ND	ND

PPI: proton pump inhibitors; CI: confidence interval; ND: not determinable

dose, considering also that, in some cases, there was a recommendation to switch to the lower dose of 110 mg.

At the end of the study, the proportion of patients over 75 years of age and on the 110 mg dose was larger in comparison to individuals of the same age on the higher dose. Some studies argue that elderly patients present a decrease in blood flow, kidney mass and function, leading to a reduction of creatinine clearance.[14,15] This, in turn, reflects the clearance of drugs eliminated through urine, such as dabigatran.[4,16] In around 67% of elderly individuals, kidney function decline relative to age was associated to the presence of cardiovascular diseases, among other risk factors.[17] In elderly patients, a great dispositional variability of drugs is particularly prominent; the complexity of interactions between comorbidity, polypharmacy, and changes related to age in drug pharmacokinetics and pharmacodynamics justifies the well-known aphorism: "start low, go slow".[17] Furthermore, age is taken into account for the calculation of the risk score for bleeding.[18]

Data shows that prescription and dose determination for the drug were given based on the risk for

Table 5 – Characterization of patients who did and did not adhere to the treatment with dabigatran in each of the four trimesters of follow-up

Trimester	1º (N=139)		2º (N=107)		3º(N=101)		4º (N=98)	
	% (N)	Relative variation (CI)	% (N)	Relative variation (CI)	% (N)	Relative variation (CI)	% (N)	Relative variation (CI)
Total								
Adherence	56.8% (79)	0.76	59.8% (64)	0.67	62.4% (63)	0.60	63.3% (62)	0.58
No Adherence	43.2% (60)	(0.60-0.96)	40.2% (43)	(0.51-0.89)	37.6% (38)	(0.45-0.81)	36.7% (36)	(0.43-0.78)
110 mg								
Adherence	15.8% (22)	0.50	17.7% (19)	0.42	20.8% (21)	0.43	16.3% (16)	0.87
No Adherence	7.9% (11)	(0.25-0.99)	7.5% (8)	(0.19-0.92)	8.9% (9)	(0.21-0.89)	14.3% (14)	(0.45-1.69)
150 mg								
Adherence	41.0% (57)	0.86	42.0% (45)	0.78	41.6% (42)	0.69	46.9% (46)	0.48
No Adherence	35.2% (49)	(0.64-1.16)	32.7% (35)	(0.55-1.10)	28.7% (29)	(0.47-1.01)	22.4% (22)	(0.31-0.73)
< 75 years								
Adherence	48.9% (68)	0.73	51.4% (55)	0.69	53.5% (54)	0.61	57.1% (56)	0.54
No Adherence	36.0% (50)	(0.56-0.97)	35.5% (38)	(0.50-0.95)	32.7% (33)	(0.44-0.85)	30.6% (30)	(0.38-0.76)
≥ 75 years								
Adherence	7.9% (11)	0.91	8.4% (9)	0.56	8.9% (9)	0.56	6.1% (6)	1.00
No Adherence	7.2% (10)	(0.40-2.07)	4.7% (5)	(0.19-1.60)	4.9% (5)	(0.19-1.60)	6.1% (6)	(0.33-2.99)
Female								
Adherence	19.4% (27)	0.85	16.8% (18)	0.89	19.8% (20)	0.55	18.4% (18)	0.72
No Adherence	16.5% (23)	(0.51-1.41)	14.9% (16)	(0.48-1.65)	10.9% (11)	(0.28-1.09)	13.3% (13)	(0.37-1.39)
Male								
Adherence	37.4% (52)	0,71	43.0% (46)	0.59	42.6% (43)	0.63	44.9% (44)	0.52
No Adherence	26.6% (37)	(0.50-1.01)	25.2% (27)	(0.40-0.87)	26.7% (27)	(0.42-0.93)	23.5% (23)	(0.34-0.79)
Dyspepsia								
Adherence	23.7% (33)	0.79	4.7% (5)	1.20	7.9% (8)	0.50	7.1% (7)	0.43
No Adherence	18.7% (26)	(0.50-1.24)	5.6% (6)	(0.38-3.81)	4.0% (4)	(0.15-1.61)	3.1% (3)	(0.11-1.61)
Minor bleeding								
Adherence	7.9% (11)	0.54	5.6% (6)	0.50	5.9% (6)	0.50	4.1% (4)	1.25
No Adherence	4.3% (6)	(0.21-1.43)	2.8% (3)	(0.13-1.95)	3.0% (3)	(0.13-1.94)	5.1% (5)	(0.34-4.52)

CI: confidence interval.

thromboembolic event and susceptibility to bleeding, respectively.[14] When the risks for stroke and hemorrhage are high, dabigatran seems to offer more clinical benefits than warfarin.[19] However, according to the study RE-LY,[14] the 150 mg dose of dabigatran determined hemorrhagic events in similar proportion, which may justify the inference. It is noteworthy that dabigatran was prescribed to some patients with a CHA_2DS_2-VASc below 2. According to Seno et al. (2014),[19] antithrombotic agents should only be administered under those circumstances, if the patients are male with a risk score of 1.

Adverse reactions to drugs are a type of adverse event considered non-avoidable and are always associated to patient harm.[20] According to Costa (2015),[21] adverse events are in general responsible for non-adherence and/or consequent therapy alteration, and are also related to treatment termination and medical suspension, according to reports. Minor bleedings are predictable adverse events in any anticoagulant treatment;[22] however, in the present study, its incidence decreased considerably throughout the trimesters. Regarding dyspepsia, its occurrence is also described in the literature in relation to dabigatran use, and that is associated to the drug's pharmaceutical formulation.[19] Gastric pH affects the solubility of some drugs and, therefore, their absorption when taken orally.[23] In the present case, the drug consists of hydroxypropylmethylcellulose capsules that hold tartaric acid granules coated with dabigatran etexilate. This medication was designed to promote an acidic microenvironment, favoring dissolution and absorption of the anticoagulant regardless of gastric pH variations.[24]

However, dyspepsia was less frequent among individuals over 75 years of age, which may highlight a mechanism that protects gastric mucosa, due to its atrophy in older patients, that leads to an elevation of the local pH.[25]

Proton pump inhibitors such as omeprazole are largely prescribed for conditions related to an increase in gastric acidity.[26] Some show the association between dabigatran and gastroprotective agents, not only proton pump inhibitors, but also histamine H2-receptor antagonists.[27,28] These therapeutic associations were also observed in the present work and may explain the reduction of dyspepsia occurrences.[27,28] However, changes in gastric pH may alter the drug's solubility, and proton pump inhibitors have proven able to decrease serum concentrations of dabigatran, even though the interaction is not considered clinically significant.[24] Apparently, such associations did not compromise the anticoagulant's effectiveness in the present study because no thromboembolic events were recorded.

Dyspepsia syndrome is expected with the use of antidiabetic[29] and antiplatelet agents, especially those that decrease the biosynthesis of prostaglandins.[30,31] Maybe because of that, patients on such drugs have not associated dyspepsia to the use of dabigratan, as described by Sherid et al. (2014).[32]

Tominaga et al. (2016)[33] reported the association between autonomic activity alterations and dyspepsia symptoms, concluding that Tofisopam, a phosphodiesterase inhibitor that elevates intracellular levels of cyclic nucleotides,[34] can help patients with functional dyspepsia. Since beta-blockers impede adrenergic receptor activation by endogenous agonists, thus decreasing cytosolic levels of cyclic nucleotides,[35] we can relate this mechanism to the higher prevalence of dyspepsia observed in users of this drug class.

In the present study, the occurrence of adverse events does not seem to have influenced adherence to anticoagulant therapy. Literature describes that emotional problems such as depression may be associated to a lack of treatment adherence, and that men are less susceptible to stress and alterations in mental health.[36] That may explain the higher percentage of adherence to treatment among male patients. The literature also suggests that, in general, older patients adhere less to drug treatments.[37,38] Indeed, the proportion of patients who adhered to the treatment was higher than that of those who did not among individuals under 75 years of age. The literature also suggests that the dose of the drug may impact on the patient's decision to adhere or not to a treatment, though the source of this conclusion is not available.[37] In this study, in the first nine months of follow-up, the percentage of those who did adhere to the treatment was higher among users of dabigatran 110 mg. However, in the fourth trimester, the percentage of adherence was higher among those on 150 mg.

Since there was no occurrence of major bleeding or thromboembolic events, this medication can be associated to safety and effectiveness, respectively.[19]

Conclusions

Dyspepsia was observed more frequently than mentioned at literature. The association of dabigatran with medication to protect the gastric mucosa seems to explain the reduction in frequency of this adverse event, while the use of beta-blockers seems to increase it. In this study, dabigatran proved to be safe and effective.

Author contributions

Conception and design of the research: Almeida FVS, Scaramello CBV. Acquisition of data: Martins LB. Analysis and interpretation of the data: Scaramello CBV. Statistical analysis: Scaramello CBV. Writing of the manuscript: Scaramello CBV. Critical revision of the manuscript for intellectual content: Martins ILF, Silva RM.

Potential Conflict of Interest

No potential conflict of interest was reported.

Sources of Funding

This study was partially funded by the Comissão de Aperfeiçoamento de Ensino Superior – CAPES – through the provision of master's scholarships.

Study Association

This article is part of the Master's thesis of Luise Barros Martins from Programa de Pós-Graduação em Ciências Cardiovasculares of Universidade Federal Fluminense.

References

1. Moreira DA, Habib RG, Andalaft R, Moraes LR, Fragata C, Reyés CA, et al. Abordagem clínica da fibrilação atrial. Rev Soc Cardiol Estado de São Paulo. 2008;18(3):205-20.
2. Magalhães LP, Figueiredo MJ, Cintra FD, Saad EB, Kuniyishi RR, Teixeira RA, et al. II Diretrizes Brasileiras de fibrilação atrial. Arq Bras Cardiol. 2016;106(4Supl.2):1-22.
3. Flato UA, Buhatem T, Merluzzi T, Bianco AC. Novos anticoagulantes em cuidados intensivos. Rev Bras Ter Intensiva. 2010;23(1):68-77.
4. Blommel ML, Blommel AL. Dabigatran etexilate: a novel oral direct thrombin inhibitor. Am J Health Syst Pharm. 2011;68(16):1506-19.
5. Ebner T, Wagner K, Wienen W. Dabigatran acylglucuronide, the major human metabolite of dabigatran: in vitro formation, stability, and pharmacological activity. Drug Metab Dispos. 2010;38(9):1567-75.
6. Ezekowitz MD, Nagarakanti R. Dabigatran in atrial fibrillation: pharmacology and clinical trials. J Interv Card Electrophysiol. 2011;32(3):173-80.
7. Bendel, SD, Bona R, Baker, WL. Dabigatran: an oral direct thrombin inhibitor for use in atrial fibrillation. Adv Ther. 2011;28(6):460-72.
8. Ganetsky M, Babu, KM, Salhanick SD, Brown RS, Boyer EW. Dabigatran: review of pharmacology and management of bleeding complications of this novel oral anticoagulant. J Med Toxicol. 2011;7(4):281-7.
9. Lombardino JG, Lowe JA 3rd. The role of the medicinal chemist in drug discovery - then and now. Nat Rev Drug Discov. 2004;3(10):853-62.
10. Ferreira FG, Polli MC, Oshima-Franco Y, Fraceto LF. Fármacos: do desenvolvimento à retirada do mercado. Revista Eletrônica de Farmácia. 2009;6(1):14-24.
11. Guido RV, Andricopulo AD, Oliva G. Planejamento de fármacos, biotecnologia e química medicinal: aplicações em doenças infecciosas. Revista Estudos Avançados. 2010;24(70):81-98.
12. Brick VS, Hossne WS, Hossne RS. Clinical research on new drugs (Phase I). Profile of scientific publications: data from the pre-clinical phase and bioethical aspects. Acta Cir Bras. 2008;23(6):531-5.
13. Obreli-Neto PR, Guidoni CM, Baldoni AO, Pilger D, Cruciol-Souza JM, Gaeti-Franco WP, et al. Effect of a 36-month pharmaceutical care program on pharmacotherapy adherence in elderly diabetic and hypertensive patients. Int J Clin Pharm. 2011;33(4):642-9.
14. Rowe JW, Andres R, Tobin JD, Norris AH, Shock NW. The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. J Gerontol. 1976;31(2):155-63.
15. Bressler R, Bahl JJ. Principles of drug therapy for the elderly patients. Mayo Clin Proc. 2003;78(12):1564-77.
16. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.
17. Shi S, Klotz U. Age-related changes in pharmacokinetics. Curr Drug Metab. 2011;12(7):601-10.
18. Senoo K, Lane D, Lip GY. Stroke and bleeding risk in atrial fibrillation. Korean Circ J. 2014; 44 (5): 281-90.
19. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al; RE-LY steering committee and investigators. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361(12):1139-51. Erratum in: N Engl J Med. 2010;363(19):1877.
20. Aizenstein ML, Tomassi MH. Problemas relacionados a medicamentos; reações adversas a medicamentos e erros de medicação: a necessidade de uma padronização nas definições e classificações. Rev Ciênc Farm Básica Apl. 2011;32(2):169-73.
21. Costa E, Giardini A, Savini M, Menditto E, Lehane E, Laosa O, et al. Interventional tools to improve medication adherence: review of literature. Patient Prefer Adherence. 2015;9:1303-14.
22. Crowther MA, Warkentin TE. Bleeding risk and the management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. Blood. 2008;111(10):4871-9.
23. Bender AD. Effect of age on intestinal absorption: implications for drug absorption in the elderly. J Am Geriatr Soc.1968;16(12):1331-9.
24. Stangier J. Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. Clin Pharmacokinetics. 2008;47(5):285-95.
25. Campos MT, Monteiro JB, Ornelas AP. Fatores que afetam o consumo alimentar e a nutrição do idoso. Rev Nutr. 2000;13(3):157-65.
26. Souza FC, Baptista TM, Marques EM, Barros RB, Scaramello CB. Omeprazole does not modulate pharmacokinetic of digoxin in patients with heart failure. Int J Cardiol. 2015;179:343-4.
27. Chan EW, Lau WC, Leung WK, Mok MT, He Y, Tong TS, et al. Prevention of dabigatran-related gastrointestinal bleeding with gastroprotective agents: a population-based study. Gastroenterology. 2015;149(3):586-95.
28. He Y, Wong IC, Li X, Anand S, Leung WK, Siu CW, et al. The association between non-vitamin K antagonist oral anticoagulants and gastrointestinal bleeding: a meta-analysis of observational studies. Br J Clin Pharmacol. 2016;82(1):285-300.
29. Smahelová A. [Dyspeptic syndrome associated with antidiabetic therapy]. Vnitr Lek. 2011;57(4):391-5.
30. Scheiman JM. Strategies to reduce the GI risks of antiplatelet therapy. Rev Cardiovasc Med. 2005;6 Suppl 4:S23-31.
31. Serebruany VL, Dinicolantonio JJ, Can MM, Pershukov IV, Kuliczkowski W. Gastrointestinal adverse events after dual antiplatelet therapy: clopidogrel is safer than ticagrelor, but prasugrel data are lacking or inconclusive. Cardiology. 2013;126(1):35-40.
32. Sherid M, Sifuentes H, Sulaiman S, Samo S, Husein H, Tupper R, et al. Risk of gastrointestinal bleeding with dabigatran: a head-to-head comparative study with rivaroxaban. Digestion. 2014;90(2):137-46.
33. Tominaga K, Fujikawa Y, Tsumoto C, Kadouchi K, Tanaka F, Kamata N, et al. Disorder of autonomic nervous system and its vulnerability to external stimulation in functional dyspepsia. J Clin Biochem Nutr. 2016;58(2):161-5.
34. Murthy VS, Mangot AG. Psychiatric aspects of phosphodiesterases: an overview. Indian J Pharmacol. 2015;47(6):594-9.
35. Munabi NC, England RW, Edwards AK, Kitajewski AA, Tan QK, Weinstein A, et al. Propranolol targets hemangioma stem cells via cAMP and mitogen-activated protein kinase regulation. Stem Cells Transl Med. 2016;5(1):45-55.
36. Ciechanowski PS, Katon WJ, Russo JE, Walker EA. The patient-provider relantionship: attachment theory and adherence to treatment in diabetes. Am J Psychiatry. 2001;158(1):29-35.
37. Griffith S. A review of the factors associated with patient compliance and the taking of prescribed medicines. Br J Gen Pract. 1990;40(332):114-6.
38. Gryfe CI, Gryfe BM. Drug therapy of the aged: the problem of compliance and the roles of physicians and pharmacists. J Am Geriatr Soc. 1984;32(4):301-7.

International Journal of Cardiovascular Sciences. 2017;30(4):343-353

REVIEW ARTICLE

Predictors of Metabolic Syndrome in the Elderly: A Review

Carolina Cunha de Oliveira,[1,2] Emanuelle Dias da Costa,[3] Anna Karla Carneiro Roriz,[4] Lilian Barbosa Ramos,[4] Mansueto Gomes Neto[1]

Programa de Pós-Graduação Medicina e Saúde – Universidade Federal da Bahia (UFBA), BA;[1] Universidade Federal de Sergipe, SE;[2] Residência em Nutrição Clínica – UFBA;[3] Programa de Pós-Graduação em Alimentos, Nutrição e Saúde – UFBA,[4] Salvador, BA – Brazil

Abstract

The article aimed to critically analyse studies which evaluated the capacity of anthropometric and clinical indicators to predict MetS in the elderly. Bibliographical research was performed using the electronic databasese Medline/PubMed, LILACS e SciELO , references from selected articles and contact with several authors. Twenty one articles involving anthropometric and clinical indicators in the elderly were analysed, using different MS criteria. Fourteen studies report anthropometric indicators, being the waist circumference (WC) and waist-to-height ratio (WHtR), described as the best MS predictors, with the area under the ROC curve (AUC) over 0.70 ($p < 0.05$). The neck circumference was also described as an alternative indicator but with less discriminatory power. Lipid accumulation product (LAP) was the parameter with the best performance to identify MS, with an AUC over 0.85 and efficiency greater than 70%. The WC, WHtR and LAP indicators were the most sensitive for predicting MS. The use of these parameters may facilitate the early identification of MS, with good accuracy and low cost. In addition, it is important to determine specific cutoff points for the elderly, since obesity alone does not appear to be a strong predictor of MS in the elderly.

Introduction

Metabolic syndrome (MetS) is defined as a set of risk factors that includes resistance to insulin, dyslipidemia, abdominal obesity and high blood pressure, and increases the risk of cardiovascular diseases and diabetes.[1,2] The most up-to-date criteria to define MetS were prepared by the International Diabetes Federation (IDF) task force.[2] In their guidelines, it has been established that abdominal obesity is no longer a compulsory component, and specific cut-off points should be used to classify waist circumference (WC) by ethnic groups, in addition to criteria for changes in glucose and lipid metabolism and high blood pressure.[2]

The use of clinical and anthropometric indicators can help to identify the presence of MetS.[3-5] Clinical indicators are those which associate biochemical parameters to analysis measurements, particularly the lipid accumulation product (LAP) and visceral adiposity index (VAI).[3,4] Anthropometric indicators include body mass index (BMI), WC, waist-to-hip ratio (WHR), waist-to-height ratio (WHtR), the sagittal abdominal indicator (SAD) and neck circumference (NC).[5,6]

The use of indicators to predict MetS may facilitate its identification in clinical practice, as they are simple, quick and functional. However, there is no consensus on the best indicator able to identify MetS in the elderly due to different functional characteristics and varied cut-off points, many of which are specific to young adults, and with different criteria for defining MetS.[1,2] Nevertheless, early identification of MetS is important in this age group since it may assist health teams to decide on strategies aimed at reducing global cardiovascular risk.[1]

This review aimed to critically analyse studies that evaluated the capability of anthropometric and clinical indicators to predict MetS in the elderly.

Keywords

Aged; Body weights and Measures; Risk Factors; Anthropometry; Obesity; Metabolic Syndrome; Indicators.

Methods

Search strategy

The search was performed on the MEDLINE/PUBMED, LILACS and SciELO bibliographic databases,

Mailing Address: Carolina Cunha de Oliveira
Rua Conego José Felix de Olieira, 485, Ap 10. Postal Code: 49035-170, Coroa do Meio, Aracaju, SE – Brazil
E-mail: carol_cunh@yahoo.com.br, carol_cunh104@hotmail.com

DOI: 10.5935/2359-4802.20170059

Manuscript received July 03, 2016; revised manuscript October 17, 2016; accepted February 28, 2017.

using the following word combinations: ("metabolic syndrome" or "syndrome X" or "plurimetabolic syndrome") and ("elderly" or "older adults" or "aged") and ("predict" or "identify" or "ability"). These expressions were searched either in combination with each other or alone. Articles of interest listed in the references were also identified and reviewed. Several authors were contacted for relevant information not provided in the articles.

Criteria for including the articles

Only original articles written in English, Spanish or Portuguese were included in the review. Articles published between January 2010 and January 2016 were selected and classic studies published on the topic prior to this period were also included. Population-based studies in the elderly or studies on institutionalised elderly people that evaluated anthropometric and clinical indicators (LAP, VAI or lipid ratios) as predictors of MetS were included.

Data extraction

After screening of titles and abstracts according to eligibility criteria, relevant articles were selected for full-text reading (Figure 1).

The following data were extracted independently: 1) characteristics of the article (authors, journal and year of publication); 2) location where the study was performed (city and country); 3) characteristics of the population studied (number of participants, sex and age range); 4) indicators studied (anthropometric indicators: BMI,

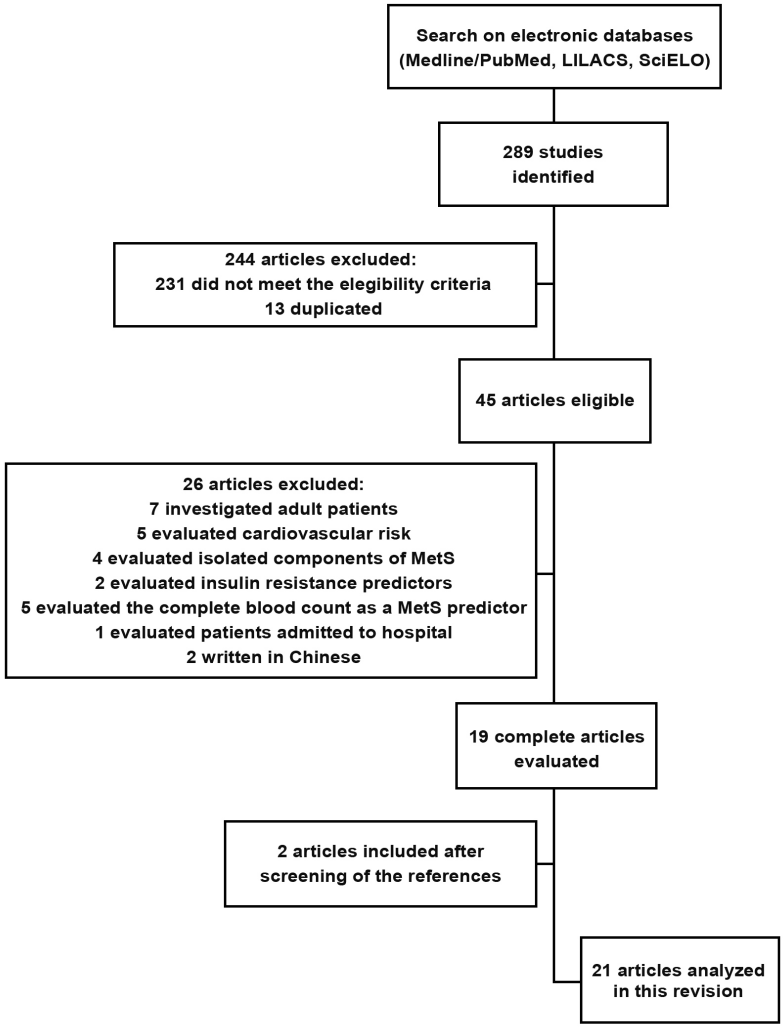

Figure 1 – *Flowchart of selection of papers for the review.*

WC, WHR, WHtR, SAD, NC and clinical indicators: LAP, VAI and lipid ratios: HDLc/TC, HDL/LDL and TG/LDL); 5) MetS classification criteria (IDF, National Cholesterol Education Program-Adult Treatment Panel III or the harmonized criteria[2] for MetS); 6) main results (area under the ROC curve: AUC; 95% CI: Confidence Interval; Cut-off points, SENS: sensitivity and SPEC: specificity).

Results

Two hundred and eighty-nine studies were identified on the bibliographic databases searched. After reading the titles and abstracts, 244 studies were excluded. Thus, 45 articles were eligible for evaluation, and 26 of these papers were excluded as: 7 presented data on a young adult population; 5 evaluated global cardiovascular risk; 4 evaluated isolated MetS components (dyslipidemia, high blood pressure, diabetes or obesity); 2 evaluated predictors of resistance to insulin; 5 evaluated complete blood count components as predictors of MetS; 1 were with patients admitted to hospital and 2 studies written in Chinese. Finally, after reviewing the bibliographic references for articles of interest, two further papers were included. Thus, 21 articles were analysed in this review (Figure 1).

Of the articles analysed, 13 discussed anthropometric indicators (Tables 1 and 2), 7 evaluated clinical indicators (LAP, VAI and lipid ratios) (Tables 3 and 4) and one

Table 1 – Studies evaluating the anthropometric indicators as predictors of metabolic syndrome in the elderly

Authors and publication year (Ref. nº.)	City, country	Number of participants (W, M)	Age range (years)	Indicator	Criteria for MetS diagnosis
Gharipour et al. 2014 [5]	Isfahan, Iran	206 men	71.85±5.44	BMI, WC*, WHR, and WHtR	2 or more factors of NCEP ATPIII without WC
Liang et al. 2013 [7]	Canton, China	4706 women	≥ 50	WC*, WHR, WHtR, BMI	Harmonized criteria for MetS
Yan et al. 2014 [8]	Shanghai, China	2092 subjects (1121 W, 971 M)	≥ 65	NC	Harmonized criteria for MetS
Guasch-Ferré et al. 2012 [9]	Spain	7447 subjects	M: 55-80 W: 60-80	WC*, WHR, WHtR, BMI	Harmonized criteria for MetS
Chu et al. 2012 [11]	Taipei, Taiwan	2848 women	≥65	BMI, WC*, WHR and WHtR	IDF without WC
Gharipour et al. 2013 [12]	Isfahan, Iran	468 subjects (232 W; 236 M)	> 60	WC*, BMI, WHR	NCEP ATPIII
Zeng et al. 2014 [13]	China	221270 subjects (84014 W; 137256 M)	45-79	BMI, WC*, WHtR	2 or more factors
Paula et al. 2012 [14]	Viçosa, Brazil	113 women	60-83	BMI, WC†, WHR, SS	NCEP ATPIII without WC
Risérus et al. 2010 [16]	Stockholm, Sweden	4032 subjects (2096 W; 1936 M)	≥ 60	SAD, BMI, WC* and WHR	Cardiometabolic risk score
Sharda et al. 2014 [17]	Kota, India	400 subjects (200 W, 200 M)	60-90	SAD	IDF
Aoi et al. 2014 [18]	Mihara, Japan	64 women	63.6 ± 7.1	BMI, %BF, WC† and NC	MetS components
Limpawattana et al. 2016 [19]	Khon Kaen, Thailand	587 subjects (386 W, 201 M)	≥ 50	NC	NCEP ATPIII and IDF
Hoebel et al. 2012 [20]	North West Province South Africa	409 subjects (207 W, 202 M)	25-65	NC, WC*	IDF
Liu et al. 2013 [21]	Beijing, China	1698 subjects (593 W; 1689 M)	20-79	BMI, FMI and %BF	NCEP ATPIII

W: women; M: men; MetS: metabolic syndrome; IDF: International Diabetes Federation; NCEP ATPIII: National Cholesterol Education Programme Adult Treatment Panel III; BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; SAD: sagittal abdominal diameter; NC: neck circumference; SS: sum of the four skinfolds; %BF: percentage of body fat; FMI: fat mass index.

** plane the midpoint between the lower costal rib and the iliac crest, perpendicular to the long axis of the trunk. † at the level of the umbilicus.*

Table 2 – Cut-offs and areas under the ROC curve, sensitivity and specificity of anthropometric indicators to determine metabolic syndrome in the elderly

Authors and publication year (Ref. nº.)	Indicator	Men				Women			
		AUC (95% CI)	Cut-off point	Sens (%)	Spec (%)	AUC (95% CI)	Cut-off point	Sens (%)	Spec (%)
Gharipour et al. 2014 [5]	WC	0.683 (0.606-0.761)	94.5 cm	64.0	68.0				
	WHR	0.645 (0.563-0.727)	0.96	6.0	69.0				
	BMI	0.641 (0.561-0.722)	26.65 kg/m²	48.0	76.0				
	WHtR	0.680 (0.602-0.758)	58.66	52.0	79.0				
Liang et al. 2013 [7]	WC					0.76	79.5 cm	72.7	76.7
	WHR					0.70	0.86	62.8	72.1
	WHtR					0.74	0.53	67.6	72.9
	BMI					0.71	22.47 kg/m²	64.8	67.3
Yan et al. 2014 [8]	NC	0.76	> 38 cm	80.0	55.0	0.73	> 35 cm	75.0	67.0
Guasch-Ferré et al. 2012 [9]	WHtR	0.74 (0.72-0.75)	Presented results without stratification by sex						
	WC	0.72 (0.71-0.73)							
	BMI	0.69 (0.68-0.70)							
Chu et al. 2012 [11]	WHtR					0.66 (0.58-0.74)	0.54	70	70
	WC					0.68 (0.60-0.76)	82.4 cm	75	69
	WHR					0.63 (0.56-0.71)	0.84	58	72
	BMI					0.58 (0.50-0.68)	24.4 kg/m²	78	60
Gharipour et al. 2013 [12]	WC	0.78 (0.70-0.85)	92.0cm	81.4	55.8	Presented results without stratification by sex			
	WHR	0.76 (0.68-0.83)	0.93	82.9	52.3				
	BMI	0.77 (0.70-0.84)	28.8 kg/m²	80.0	61.6				
Zeng et al. 2014 [13]	BMI	0.640 (0.648-0.666)ᶜ	24.2 kg/m² ᶜ	69.1	54.3	0.637 (0.624-0.650)ᶜ	23,3 kg/m²	70.4	49.7
		0.665 (0.654-0.675)¶	23.3 kg/m² ¶	71.7	52.3	0.665 (0.648-0.682)¶	23,5 kg/m²	65.3	59.9
	WC	0.640 (0.631-0.654)ᶜ	83.5 cm	74.3	45.8	0.641 (0.628-0.645)ᶜ	78,5 cm	65.2	55.6
		0.646 (0.636-0.657)¶	82.3 cm	74.0	47.3	0.668 (0.651-0.685)¶	78,5 cm	70.1	54.7
	WHtR	0.645 (0.636-0.654)ᶜ	0.52	62.3	58.4	0.640 (0.627-0.653)ᶜ	0,49	76.0	44.5
		0.651 (0.641-0.662)¶	0.50	71.9	50.2	0.659 (0.642-0.676)¶	0,52	65.2	59.6

To be continued

Continuation

Paula et al. 2012 [14]	WC					0.694 (0.600-0.777)	92.0 cm	80	58.2
	BMI					0.619 (0.523-0.708)	25.4 kg/m²	66.7	55.1
	WHR					0.752 (0.662-0.829)	0.98	80	59.2
	SS					0.669 (0.574-0.726)	108 mm	66.7	64.3
Risérus et al. 2010 [16]	SAD	0.80 (0.77-0.82)	22.2 cm			0.77 (0.75-0.80)	20.1 cm		
	WC	0.78 (0.75-0.80)	100 cm			0.77 (0.75-0.80)	88.4 cm		
	WHR	0.74 (0.71-0.77)	0.97			0.76 (0.74-0.79)	0.82		
	BMI	0.78 (0.76-0.81)	27.9 kg/m²			0.74 (0.72-0.77)	27.6 kg/m²		
Sharda et al. 2014 [17]	SAD		> 22 cm	88.0	83.0		> 20 cm	87.0	80.0
Aoi et al. 2014 [18]	NC	NC was associated with BMI (r = 0.747, p < 0.0001), %BF (r = 0.715, p < 0.0001), TG (r = 0.276, p = 0.028), decrease in HDLc (r = –0.401, p < 0.001) and HbA1c (r = 0.298, p = 0.019), HOMA-R and leptin (r = 0.488, p < 0.001)							
Limpawattana et al. 2016 [19]	NC	0.84 (0.79-0.90)‡ 0.71 (0.64-0.78)§	> 39 cm‡	70.89	81.15	0.79 (0.75-0.84)‡ 0.77(0.72-0.82)§	> 33 cm‡	86.54	59.39
Hoebel et al. 2012 [20]	NC	0.70 (0.50-1.00)* 0.70 (0.60-0.90)†	> 35 cm* > 41 cm†			0.60 (0.40-0.80)* 0.80 (0.70-0.90)†	> 35 cm* > 33 cm†		
Liu et al. 2013 [21]	BMI	0.904 (0.882-0.925)	27.45 kg/m²	80.6	84.3	0.869 (0.869-0.928)	23.85 kg/m²	92.7	72.9
	BF	0.883 (0.859-0.908)	23.95%	84.1	7.8	0.855 (0.818-0.892)	31.35%	77.1	81.4
	FMI	0.920 (0.900-0.940)	7.00 kg/m²	80.2	86.9	0.898 (0.869-0.927)	7.90 kg/m²	78.9	85.7

AUC: area under ROC curve; 95% CI: 95% confidence interval; Sens: sensitivity; Spec: specificity; BMI: body mass index; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; SAD: sagittal abdominal diameter; NC: neck circumference; SS: sum of the four skinfolds; %BF: percentage of body fat; FMI: fat mass index; HbA1c: glycated haemoglobin.
** Older African group; † Older caucasian group; ‡ IDF Criteria; § NCEP ATP III Criteria; ≠60-69 years; ¶ 70-79 years.*

article[7] compared anthropometric indicators and lipid ratios to predict MetS in the elderly (and hence is cited in anthropometric and clinical indicators' tables).

The IDF's and the NCEP-ATP III's criteria were most commonly used criteria for definition of MetS). Only 5 articles used the most recent harmonized criteria for MetS.[7-10] The harmonized criteria states that obesity itself is not a prerequisite for diagnosis of MetS, which should be established based on the presence of any 3 or 5 risk factors (among which obesity is included).

Anthropometric indicators

Fourteen studies reported anthropometric indicators as predictors of MetS (Tables 1 and 2). Among the anthropometric indicators, those most cited were BMI, WC and WHR. The most recent studies analysed WHtR, SAD and NC.

The majority of the papers[5,7,11-13] which evaluated anthropometric indicators highlight WC and WHtR as the best predictors of MetS in the elderly, when compared to BMI and WHR.

Table 3 – Studies evaluating the clinical indicators as predictors of metabolic syndrome in the elderly

Authors and publication year (Ref. nº.)	City, country	Number of participants	Age range (anos)	Indicator	Criteria for MetS diagnosis
Liang et al. 2013 [7]	Canton, China	4706 women	≥ 50	TG/HDL, HDL/TC, HDL/LDL	Harmonized criteria for MetS
Arthur et al. 2012 [10]	Kumasi, Ghana	250 women	20-78	TG/HDL, HDL/TC	Harmonized criteria for MetS
Tellechea et al. 2009 [22]	Buenos Aires, Argentina	601 men	18-65	LAP	NCEP ATPIII
Taverna et al. 2011 [23]	Province of Segovia, Central Spain	768 subjects (416 W; 352 M)	36-77	LAP, TG/HDL, TG, WC and BMI	NCEP ATPIII vs. IDF
Chiang & Koo 2012 [24]	Taiwan	513 subjects (247 W; 266 M)	> 50	LAP, WHtR, BMI and WC	MetS criteria for Taiwanese people
Ejike 2011 [25]	Abia State, Nigeria	40 men	65-84	LAP, VAI, BMI, WHtR and WHR	IDF
Motamed et al. 2015 [26]	Amol, Iran	5511 subjects (2392 W; 3119 M)	18-90	LAP, WC, BMI, WHtR, WHR	IDF
Amato et al. 2011 [27]	Alcamo, Italy	1764 subjects (1179 W; 585 M)	16-99	VAI	NCEP ATPIII

W: women; M: men; MetS: metabolic syndrome IDF: international diabetes federation; NCEP ATPIII: National Cholesterol Education Programme Adult Treatment Panel III; LAP: lipid accumulation product; VAI: visceral adiposity index; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio. BMI: body mass index; HDLc/TC: HDL-cholesterol to total cholesterol ratio; HDL/LDL:HDL-cholesterol to LDL: cholesterol ratio; TG/LDL: triglyceride to HDL: cholesterol ratio.

The works of Liang et al.[7] and Guasch-Ferré et al.[9] reported an AUC over 0.70 for WC and WHtR to detect MetS, considering the harmonized criteria for MetS. For women, Liang et al.[7] identified the cut-off points of 79.5 cm for WC (sens: 72.7%; spec: 76.7%) and 0.53 for WHtR (sens: 67.6%; spec: 72.9%), with efficiency higher than 70%. Zeng et al,.[13] evaluating the presence of a minimum of two MetS components and stratifying the results by sex and age, observed similar AUCs and cut-off points for elderly women at the age range of 60-69 and 70-79 years (Table 2).

Among the indicators with unsatisfactory performance, Paula et al.[14] established that the BMI and the sum of four skinfolds were the anthropometric parameters of adiposity which presented the least efficiency in identifying MetS.

Another indicator cited was SAD, which is able to estimate the excess of visceral fat and, consequently, is a better predictor of cardiometabolic risk than classic indicators.[15] Only two studies[16,17] evaluated SAD in the elderly; Sharda et al.[17] aimed to identify the best SAD cut-off points to predict MetS, and suggested the cut-off points of 22 cm for men and 20 cm for women, with sensitivity and specificity higher than 80% for both sexes. Similar cut-offs were found by Risérus et al.[16] using a cardiometabolic risk in elderly subjects.

In relation to NC, the articles analysed its performance in identifying MetS and its isolated components. Aoi et al.[18] showed that the increase in NC is associated to a rise in metabolic risk factors, such as resistance to insulin (leptin, HbA1c and HOMA-IR) and lipid profile (TG and HDL).

In the studies[8,19,20] which evaluated the predictive capacity of the NC, the cut-off points suggested by the authors were quite similar, varying between 35 and 41 cm for men and 33 and 35 cm for women (Table 2). Hoebel et al.[20] observed that white men presented a higher cut-off point (41 cm) when compared to black men (35 cm). The cut-off points for women were similar between white and black women, although the cut-off point for black women did not predict MetS, in contrast to what was observed for men. Limpawattana et al.[19]

Table 4 – Cut-offs and areas under the ROC curve, sensitivity and specificity of clinical indicators to determine metabolic syndrome in the elderly

Authors (Ref. nº.)	Indicators	Men				Women			
		AUC (95% CI)	Cut-off point	Sens (%)	Spec (%)	AUC (95% CI)	Cut-off point	Sens (%)	Spec (%)
Amato et al. 2010 [4]	VAI	0.840 (0.98-1.00)‡ 0.783 (0.73-0.82)§	1.93 2.00	77.0 68.5	82.3 76.0	No stratification by sex			
Liang et al. 2013 [7]	TG/HDLc					0.84	0.88	77.7	76.0
	HDLc/TC					0.73	0.73	70.1	64.6
	HDLc/LDLc					0.74	0.68	78.3	65.7
Arthur et al. 2012 [10]	TG/HDLc					0.80 (0.70–0.90)	0.61	87.2	80.0
	HDLc/TC					0.80 (0.70–0.90)	0.34	96.6	83.3
Tellechea et al. 2010 [22]	LAP	0.91 (p < 0.05)	53.63	83.0	83.0				
Taverna et al. 2011 [23]	LAP	61-70 years old: 0.89 (0.82-0.97)† 0.84 (0.74-0.93)* 71-77 years old: 0.89 (0.77-1.01)† 0.91 (0.82-1.00)*	> 51.82† > 48.09*			61-70 years old: 0.79 (0.69-0.90)† 0.78 (0.67-0.89)Δ 71-77 years old: 0.88 (0.76-0.99)† 0.85 (0.74-0.99)*	> 33.28† > 31.7*		
	WC	61-70 years old: 0.82 (0.72-0.93)†				61-70 years old: 0.78 (0.68-0.87)†			
	BMI	0.85 (0.75-0.95)†				0.74 (0.63-0.85)†			
Chiang & Koo 2012 [24]	LAP	0.916 (0.880-0.953)	31.6	88.0	82.0	0.901 (0.855-0.946)	31.6	66.0	93.0
	WHtR	0.827 (0.762-0.892)				0.819 (0.755-0,883)			
	BMI	0.776 (0.709-0.844)				0.793 (0.726-0.859)			
	WC	0.825 (0.760-0.890)				0.817 (0.755-0.879)			
Ejike 2011 [25]	LAP	0.937 (p < 0.05)	43.91	100	81.0				
	VAI	0.640	4.44	67.0	84.0				
	BMI	0.793	30.47 kg/m²	100	73.0				
	WHtR	0.905 (p < 0.05)	0.61	100	78.0				
	WHR	0.635	1.08	67.0	76.0				
Motamed et al. 2015 [26]	LAP	0.901 (0.890-0.913)	39.89	86.0	79.6	0.904 (0.892-0.916)	49.71	85.2	82.3
	WC	0.907 (0.897-0.917)				0.782 (0.764-0.801)			
	BMI	0.862 (0.849-0.876)				0.701 (0.680-0.722)			
	WHtR	0.878 (0.868-0.889)				0.788 (0.769-0.806)			
	WHR	0.840 (0.826-0.855)				0.785 (0.766-0.803)			

AUC: area under ROC curve; 95% CI: 95% confidence interval; Sens: sensitivity; Spec: specificity; LAP: Lipid Product Accumulation; VAI: Visceral Adiposity Index; WC: waist circumference; WHR: waist-to-hip ratio; WHtR: waist-to-height ratio; BMI: body mass index; HDLc/TC: HDL-cholesterol to total cholesterol ratio; HDL/LDL: HDL-cholesterol to LDL: cholesterol ratio; TG/LDL: triglyceride to HDL-cholesterol ratio.
** IDF Criteria; † NCEP ATP III Criteria; ‡ 52 – 66 years old; § > 66 years old.*

and Yan et al.[8] presented similar cut-off points for NC to predict MetS in individuals aged over 50 and 65 respectively, and Limpawattana et al.[19] showed an efficiency over 72% for the cut-off point suggested for men (sens: 70.89%; spec: 81.15%) and women (sens: 86.54%; spec: 59.39%).

A parameter that has been insufficiently investigated was the Fat Mass Index (FMI), which is normalizes body fat for individual's height. This index has been suggested to independently evaluate body fat from changes in fat free mass. In the study performed by Liu et al.,[21] FMI was the parameter with the highest AUC, and high FMI showed significantly higher odds ratio for MetS than the low FMI in both sexes. These authors suggested that a FMI of 7.00 kg/m² for men and 7.90 kg/m² for women, evaluated by bioelectrical impedance analysis, could predict the presence of MetS.

Clinical indicators

Tables 3 and 4 demonstrate the characteristics and results, respectively, of the eight studies which evaluated LAP and VAI clinical indicators and lipid ratios as predictors of MetS according to NCEP and IDF criteria and harmonized criteria for MetS.

LAP is an indicator proposed to estimate lipid concentration in adults, described for the first time by Kahn.[3] It is an emerging cardiovascular risk index based on the product of WC multiplied by fasting triglyceride concentration. LAP has proven to be a reliable marker for cardiovascular disease in adults, outperforms other predictors of this risk as BMI.[3] Most of the studies analysed evaluated a mixed population, stratified by sex and/or age range. The cut-off point for LAP suggested by the authors[22-26] varied from 31.6 to 51.8, with a difference between the sexes (Table 4). Among men, the LAP AUC to predict MetS varied from 0.84 to 0.937, while for women the lowest AUC was 0.78 and highest was 0.904 (Table 4).

Taverna et al.[23] reported a lower AUC for men and women in the 61-70 age range, considering the IDF criteria (area under the curve, AUC: 0.84; 95% CI: 0.74-0.93 for men and 0.78; 95% CI: 0.76-0.99 for women) when compared to the other studies.

Ejike CECC[25] investigated LAP as a predictor of MetS in the elderly (aged between 65 and 84); the authors reported an AUC of 0.937 (p=0.013) and suggested a LAP cut-off point of 43.9 (sens: 100%; spec: 81%). Tellechea et al.[22], Chiang & Koo[24] and Motamed et al.[26] also observed the high predictive capacity of LAP to identify MetS (AUC higher than 0.90). Among these studies, the lowest LAP cut-off point to identify MetS was reported by Chiang & Koo[24] (31.6 for both sexes).

VAI is a gender-specific, empirical-mathematical model based on a combination of anthropometric measurements (WC and BMI) with biochemical parameters (TG and HDLc), which may be and indicator of fat distribution and function.[4] The Alkam Metabolic Syndrome Study[4] introduced VAI as a new marker of adipose tissue dysfunction, independently associated with cardiovascular events, which was not observed for WC and BMI. Only two studies investigated this indicator in MetS.[25,27] For Amato et al.[27], a VAI value higher than 2.00 (sens: 68.5% and spec: 76.0%) for individuals aged over 66 was able to predict MetS. However, in the study by Ejike CECC,[25] VAI showed an AUC of 0.640 but without statistical significance (p = 0.426), suggesting a cut-off point higher than 4.4, with relatively better sensitivity and specificity to identify MetS in the elderly (sens: 67% and spec: 84%).

Two papers[7,10] described the results of lipid ratios, with different cut-off points between the studies. Arthur et al.[10] observed that the TG/HDL and HDL/CT ratios presented AUC of 0.80 (95% IC: 0.70-0.90) for both ratios, suggesting a cut-off point of 0.61 (sens: 87.2% and spec: 80%) for the TG/HDL ratio and 0.34 (sens: 96.6% and spec: 83.3%) for the HDL/CT ratio, therefore demonstrating efficiency of over 83%.

Discussion

The anthropometric indicators that showed a better performance in identifying MetS were WC and WHtR (among the classic indicators) and NC (among the recently studied indicators). Regarding the clinical parameters, LAP was the best indicator, followed by the HDL/CT ratio.

An important point to be discussed is the criteria used to define MetS (IDF, NCEP ATPIII and harmonized criteria), which may justify the diversity of results discussed in this review. In addition, the use of different criteria and measurement techniques, particularly in relation to WC, does not ensure comparability between the studies.

WC and WHtR were the best parameters evaluated,[5,7,9,13] with WC showing higher sensitivity among the obesity indexes. In addition, it was observed that the WC cut-off points suggested were lower than those proposed by the MetS criteria used, revealing that non-specific cut-off points for ethnic and age groups can underestimate the presence of MetS, depending on the criterion used for its classification. However, Chu et al.[11] observed that WC

and WHtR showed similar results to BMI and WHR, with an AUC lower than 0.70 to detect a minimum of three MetS criteria in women. This divergence could be attributed to the age of the elderly (average of 71.9 years), with high prevalence of other comorbidities, apart from obesity, that contribute to the development of MetS. Therefore, obesity appears not to be a decisive criterion for MetS detection in this age range.

A further indicator discussed in the literature is SAD. Although very few studies have evaluated this indicator as a predictor of MetS, the cut-off points suggested by Risérus et al.[16] and Sharda et al.[17] are in line with other studies that evaluated SAD as a predictor of visceral fat.[15,28] Despite being related to visceral abdominal fat deposits, SAD has not been widely used in clinical practice since it requires a specific measuring instrument (abdominal caliper – Holtain, Ltd, Dyfed, Wales, U.K).

NC was also evaluated, with similar cut-off points suggested by the authors,[8,19,20] which can be explained by the fact that this measurement is little affected by aging-related changes in body composition. The association between NC and MetS may be related to the fact that subcutaneous fat in the neck area is responsible for higher systemic release of free fatty acids.[19] This excess of free fatty acids is associated with resistance to insulin, hypertriglyceridemia, vascular lesion and high blood pressure, and could predict MetS.

Differences between sexes and ethnic groups were reported in the study by Hoebel et al.[20] The authors observed that a NC cut-off point of 35 cm was not able to predict MetS in black women, in contrast with what was observed in men, suggesting a concept of "healthy obesity". However, a limitation of this study was that the authors considered individuals aged between 46 and 65 as the elderly group and, for this reason, their results cannot be extrapolated to individuals aged over 65. Altogether, the studies[8,18-20] suggested the use of NC, as it is a simple and practical anthropometric parameter, able to identify MetS. Another advantage of the NC is the fact that it is not affected during respiratory movement or in the postprandial period.

FMI was only discussed in the study by Liu et al.[21] Although the authors suggested a cut-off point, it is worth pointing out that there was no stratification by age group in the data analysis. In addition, the study was conducted in China, in a smaller population with brevilineal biotype, which limit the extrapolation of results to other populations.

The studies included showed that the cut-off points for obesity indicators need to be specific for the elderly, with higher values when compared to other age groups, as obesity does not appear to be a strong predictor of MetS in the elderly.

With regards to clinical indicators, LAP was the parameter most discussed in the studies. Kahn[3] highlights that the WC and TG levels tend to increase with age, accumulating over time. From this perspective and considering that lipid accumulation intensifies cardiometabolic consequences, the use of LAP seems an advantageous approach in evaluating MetS and cardiovascular risk.

The cut-off points for LAP suggested by the studied showed a wide variety, which could be justified by ethnic diversity, extensive age ranges and different criteria used to define MetS. In addition, two studies[22,26] did not adequately define the age group of the elderly. While Motamed et al.[26] did not stratify the results between adults and the elderly, Tellechea et al.[22] considered the elderly group to be aged between 45 and 65. These facts limit the understanding of this indicator's performance, specifically among the elderly.

Although Taverna et al.[23] has reported the lowest LAP AUC for the elderly aged between 61-70 years when compared with other studies, these authors show a better performance of LAP as a predictor of MetS in the elderly. Besides, although Ejike CECC[25] demonstrated good results using the LAP indicator, a small sample (only 40 men) was included, which was an important limitation of the study.

The lowest LAP cut-off point to predict MetS suggested by Chiang & Koo,[24] could be related to the criterion used to define MetS and the physical characteristics of the population evaluated. The capacity of LAP to identify MetS, compared with that of other parameters, is associated to the fact that this indicator reflects anatomical and physiological alterations associated to visceral fat and its accumulation,[22,25] indicating that, regardless of how excess lipids are stored, it will be identified by LAP.[25]

Another clinical indicator also related to the dysfunction of the adipose tissue is VAI, which uses WC, BMI, TG and LDL measurements for its calculation. Only two studies[25,27] have analysed its performance and proposed a VAI cut-off point to identify MetS. However, the cut-off points suggested diverged among the authors. It is of note that three of the variables on which VAI is based (WC, TG and HDL) are also MetS components, which makes the use of this index in patients with clear MetS pointless.[29] The studies[7,10] using lipid ratios showed that the use of this indicator in

isolation is not able to identify MetS, particularly among the elderly, but rather to identify isolated cardiovascular risk factors.

The results were clear in showing that WC, WHtR and LAP indicators were the most sensitive ones for predicting MetS. Therefore, the use of these parameters may facilitate the early identification of MetS through easily-applied, precise and low cost diagnostic methods. The use of these indicators by health professionals is important to optimise MetS prevention and treatment, and to minimize its complications.

To summarise, the studies included propose different indicators to predict MetS. However, the cut-off points suggested vary between each other, as they are linked to different populations, with different age and ethnic characteristics. Further studies are required to identify the best practical, validated method to predict MetS. Also, studies comparing different indicators are needed, considering specific aspects, such as sex, well-defined age ranges and ethnic groups.

Different MetS classification criteria have been adopted, which makes the comparison between the studies problematic and the standardisation of the criteria essential. In addition, there is no consensus on the best indicator to predict MetS in the elderly, and studies in this population is still scare. These data affect the understanding of the indicators' performance in predicting MetS in this age group.

The most of these studies presented to methodological differences and study designs, as well as limitations inherent to observational studies, which make the comparison between results and the control of population biases difficult.

Conclusion

Analysis of the studies included in this review allowed us to infer that the WC, WHtR and LAP indicators presented the best predictive power for MetS in the elderly because they are strongly related to visceral abdominal fat deposits. However, the disparate values between the studies substantiated that the prevalence of other comorbidities, rather than obesity, may be contributing to the development of MetS in this population. Thus, the results revealed that the distribution of abdominal fat, instead of overweight appears to be a fundamental criterion for this age group, but the distribuition of abdominal fat. The need to identify a simple method which facilitates the approach and detection of high risk for MetS in the elderly is highlighted, allowing the early prevention of cardiovascular events.

Author contributions

Conception and design of the research: Oliveira CC, Roriz AKC, Ramos LB, Gomes Neto M. Acquisition of data: Oliveira CC, Costa ED. Analysis and interpretation of the data: Oliveira CC, Roriz AKC, Ramos LB, Gomes Neto M. Statistical analysis: Oliveira CC. Obtaining financing: Ramos LB. Writing of the manuscript: Oliveira CC, Costa ED, Gomes Neto M. Critical revision of the manuscript for intellectual content: Oliveira CC, Roriz AKC, Ramos LB, Gomes Neto M.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by FAPESB - Fundação de Amparo à Pesquisa do Estado da Bahia (parecer nº 0007/2013).

Study Association

This article is part of the thesis of Doctoral submitted by Carolina Cunha de Oliveira, from Programa de Pós Graduação em Medicina e Saúde da Universidade Federal da Bahia.

References

1. Akbulut G, Köksal E, Bilici S, Acar Tek N, Yildiran H, Karadag MG, et al. Metabolic syndrome (MS) in the elderly: A cross sectional survey. Arch Gerontol Geriatr. 2011;53(3):e263–6.
2. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato K A, et al. Harmonizing the Metabolic Syndrome: A Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International. Circulation. 2009;120(16):1640–5.
3. Kahn H. The "lipid accumulation product" performs better than the body mass index for recognizing cardiovascular risk: a population-based comparison. BMC Cardiovasc Disord. 2005;5(26):10.
4. Amato MC, Giordano C, Galia M, Criscimanna A, Vitabile S, Midiri M, et al. Visceral Adiposity Index: a reliable indicator of visceral fat function associated with cardiometabolic risk. Diabetes Care. 2010;33(4):920–2.
5. Gharipour M, Sadeghi M, Dianatkhah M, Bidmeshgi S, Ahmadi A, Tahri M, et al. The Cut-Off Values of Anthropometric Indices for Identifying Subjects at Risk for Metabolic Syndrome in Iranian Elderly Men. J Obes. 2014;2014:1–6.

6. Zhou J, Ge H, Zhu M, Wang L, Chen L, Tan Y, et al. Neck circumference as an independent predictive contributor to cardio-metabolic syndrome. Cardiovasc Diabetol. 2013;12:76.

7. Liang H, Chen X, Chen Q, Wang Y, Wu X, Li Y, et al. The metabolic syndrome among postmenopausal women in rural canton: prevalence, associated factors, and the optimal obesity and atherogenic indices. PLoS One. 2013;8(9):e74121.

8. Yan Q, Sun D, Li X, Zheng Q, Li L, Gu C, et al. Neck circumference is a valuable tool for identifying metabolic syndrome and obesity in Chinese elder subjects: a community-based study. Diabetes Metab Res Rev. 2014;30(1):69–76.

9. Guasch-Ferré M, Bulló M, Martínez-González MÁ, Corella D, Estruch R, Covas M-I, et al. Waist-to-height ratio and cardiovascular risk factors in elderly individuals at high cardiovascular Rrsk. PLoS One .2012; 7(8):e43275.

10. Arthur FKN, Adu-Frimpong M, Osei-Yeboah J, Mensah FO, Owusu L. Prediction of metabolic syndrome among postmenopausal Ghanaian women using obesity and atherogenic markers. Lipids Health Dis. 2012;11:101.

11. Chu F-L, Hsu C-H, Jeng C. Low predictability of anthropometric indicators of obesity in metabolic syndrome (MS) risks among elderly women. Arch Gerontol Geriatr. 2012;55(3):718–23.

12. Gharipour M, Sarrafzadegan N, Sadeghi M, Andalib E, Talaie M, Shafie D, et al. Predictors of metabolic syndrome in the iranian population: waist circumference, body mass index, or waist to hip ratio? Cholesterol. 2013;2013:198384.

13. Zeng Q, He Y, Dong S, Zhao X, Chen Z, Song Z, et al. Optimal cut-off values of BMI, waist circumference and waist:height ratio for defining obesity in Chinese adults. Br J Nutr. 2014;112(10):1735–44.

14. Paula HA A, Ribeiro RCL, Rosado LE, Abranches MV, Franceschini S C. Classic anthropometric and body composition indicators can predict risk of metabolic syndrome in the elderly. Ann Nutr Metab. 2012;60(4):264–71.

15. Carneiro Roriz AK, Santana Passos LC, Cunha de Oliveira C, Eickemberg M, de Almeida Moreira P, Ramos Sampaio L. Discriminatory power of indicators predictors of visceral adiposity evaluated by computed tomography in adults and elderly individuals. Nutr Hosp 2014;29(6):1401–7.

16. Risérus U, de Faire U, Berglund L, Hellénius M-L. Sagittal abdominal diameter as a screening tool in clinical research: cut-offs for cardiometabolic risk. J Obes. 2010;Pii:757939.

17. Sharda M, Nagar D, Soni A. Sagittal abdominal diameter as a predictor of metabolic syndrome in the elderly. J Indian Acad Geriatr. 2014 Mar;10:5–9.

18. Aoi S, Miyake T, Harada T, Ishizaki F, Ikeda H, Nitta Y, et al. Neck circumference has possibility as a predictor for metabolic syndrome in postmenopausal women. Hiroshima J Med Sci. 2014;63(4):27–32.

19. Limpawattana P, Manjavong M, Sopapong R. Can neck circumference predict metabolic syndrome? An experience from a university community. Endocr Pract. 2016;22(1):8–15.

20. Hoebel S, Malan L, de Ridder JH. Determining cut-off values for neck circumference as a measure of the metabolic syndrome amongst a South African cohort: the SABPA study. Endocrine. 2012;42(2):335–42.

21. Liu P, Ma F, Lou H, Liu Y. The utility of fat mass index vs. body mass index and percentage of body fat in the screening of metabolic syndrome. BMC Public Health. 2013;13:629.

22. Tellechea ML, Aranguren F, Martinez-Larrad MT, Serrano-Rios M, Taverna MJ, Frechtel GD. Ability of lipid accumulation product to identify metabolic syndrome in healthy men from Buenos Aires. Diabetes Care. 2009;32(7):e85.

23. Taverna MJ, Martinez-Larrad MT, Frechtel GD, Serrano-Rios M. Lipid accumulation product: a powerful marker of metabolic syndrome in a healthy population. Eur J Endocrinol .2011;164(4):559–67.

24. Chiang J-K, Koo M. Lipid accumulation product: a simple and accurate index for predicting metabolic syndrome in Taiwanese people aged 50 and over. BMC Cardiovasc Disord. 2012;12:78.

25. Ejike CECC. Lipid accumulation product and waist-to-height ratio are predictors of the metabolic syndrome in a nigerian male geriatric population. J Rural Trop Public Health. 2011;10:101–5.

26. Motamed N, Razmjou S, Hemmasi G, Maadi M, Zamani F. Lipid accumulation product and metabolic syndrome: a population-based study in northern Iran, Amol. J Endocrinol Invest .2016;39(4):375-82.

27. Amato MC, Giordano C, Pitrone M, Galluzzo A. Cut-off points of the visceral adiposity index (VAI) identifying a visceral adipose dysfunction associated with cardiometabolic risk in a Caucasian Sicilian population. Lipids Health Dis. 2011;10:183.

28. Roriz AKC, de Oliveira CC, Moreira PA, Eickemberg M, Medeiros JMB, Sampaio LR. Methods of predicting visceral fat in Brazilian adults and older adults: a comparison between anthropometry and computerized tomography. Arch Latinoam Nutr. 2011;61(1):5–12.

29. Amato MC, Giordano C. Clinical indications and proper use of the Visceral Adiposity Index. Nutr Metab Cardiovasc Dis 2013;23(8):e31–2.

VIEWPOINT

Detailing Peripheral Arterial Tonometry in Heart Failure. An Endothelial Function Evaluation

Aline Cristina Tavares,[1,2,3] Edimar Alcides Bocchi,[1] Guilherme Veiga Guimarães[1]

Instituto do Coração (InCor) do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HCFMUSP),[1] Instituto do Câncer do Estado de São Paulo,[2] Hospital Sírio-Libanês,[3] São Paulo, SP – Brazil

Introduction

Endothelium regulates cardiac function and vasomotor tone, adjusts vascular permeability, preserves blood fluidity, playing an important role in cardiovascular homeostasis.[1,2] In adults with heart failure (HF), endothelial dysfunction severity is related to diastolic dysfunction,[1,2] increase in cardiovascular risk,[1-10] heart failure,[11,12] exercise incapacity,[13] severity of cardiovascular symptoms,[6,7,10,14,15] cardiovascular events,[16] cardiac transplant and death.[17,18]

Although endothelium is at the interface between circulating cardiovascular factors and underlying organ tissues, cardiovascular and endothelial peripheral dysfunctions are not totally linked so far.[18-20] Evaluation of endothelial function appears as a tempting adjunct for cardiovascular risk stratification,[16] and understanding this matter may help having a faster approach and better screening in the cardiomyopathy field in everyday clinical practice, which brings the importance of this paper.

The objective of this study was to perform an interpretation of endothelial function development in HF patients.

Methods

Different databases (PubMed e Medline) were searched to identify the characteristics about endothelial function evaluation in both coronary and peripheral circulation, as a way to better explain the interface between endothelial dysfunction and heart failure.

Keywords

Endothelium / physiopathology; Heart Failure; Stroke Volume; Nitric Oxide.

Results

Heart failure represents the heart incapacity of performing sufficient cardiac output to satisfy all body demands[3, 20,11] either with preserved ejection fraction or not.[8,16]

There are several potential mechanisms by which endothelial dysfunction may contribute to disease progression in patients with heart failure (HF). Adult patients with HF, in New York Heart Association (NYHA) functional class II–III and more severe endothelial dysfunction would have a higher incidence of hospitalization due to decompensation of HF, cardiac transplantation, or cardiac-causing death in a 1-year follow-up than those with relatively preserved endothelium-dependent relaxation.[17]

Nonetheless, it may be a cycle dysfunction and it is not known whether endothelial dysfunction is the cause or the consequence of heart failure (Figure 1).[7-44]

Impaired availability of endothelium-derived nitric oxide (NO) contributes to this abnormal vasodilator response to physiological stimuli[7,17,20] in heart failure, both in the coronary and peripheral circulation.[13,14,23-28]

Regarding this, it is interesting to note also that a common polymorphism of endothelial NO-synthase (eNOS) shows increased vasoconstrictive response,[14,24,29] which may be associated with decreased NO-synthase (NOS) activity. This polymorphism is associated with poorer event-free survival and clinical endpoints reflecting progression of the disease in patients with heart failure.[30-32]

Mailing Address: Aline Cristina Tavares
Rua Londrina, 658. Postal Code: 09181-160, Vila Linda, Santo André, São Paulo, SP – Brazil
E-mail: alinet84@gmail.com

DOI: 10.5935/2359-4802.20170051

Manuscript received June 17, 2016; revised manuscript August 15, 2016; accepted February 24, 2017.

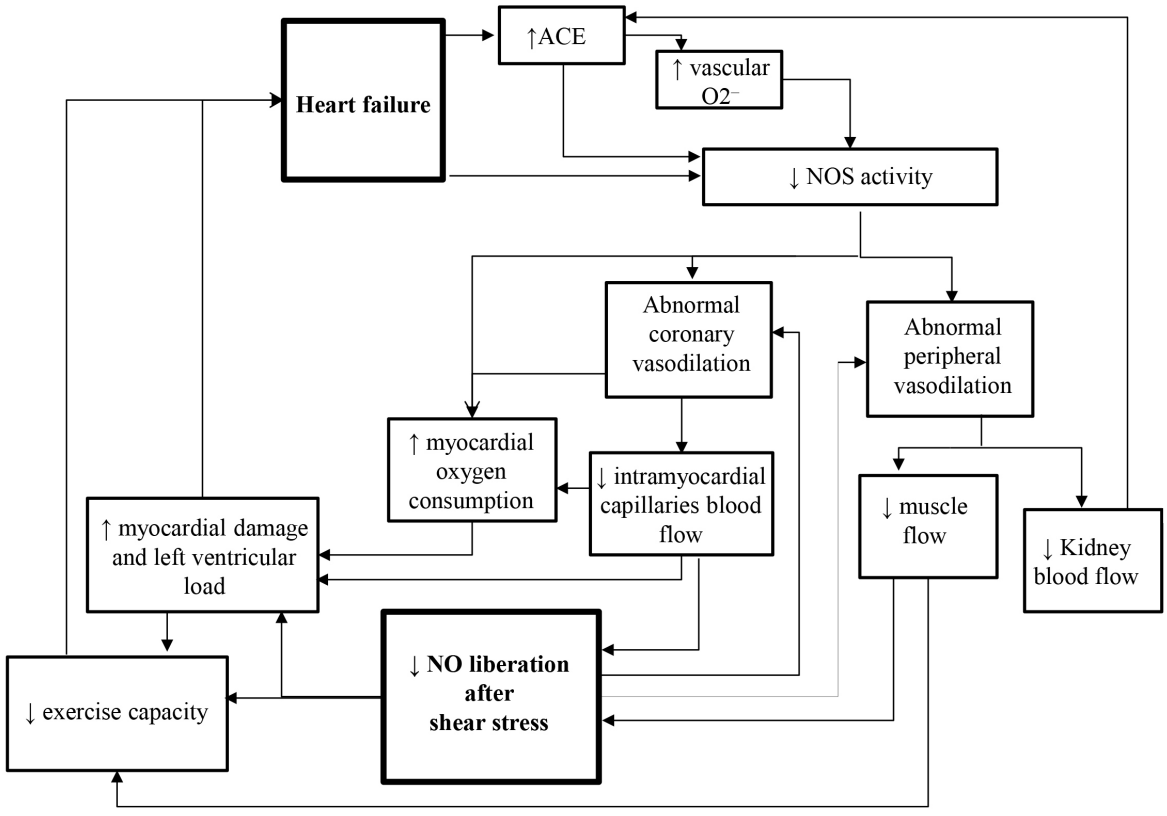

Figure 1 – *Cycle dysfunction representation between heart failure and endothelial dysfunction*
↑ increase; ↓ decrease; ACE: angiotensin converting enzyme; O2- O2-radical; NO: nitric oxide.

Therefore, endothelial dysfunction may contribute to the sympathetic tone systemically,[33-37] which contributes to exercise intolerance,[14,26,40] reduced capillary density in cardiac muscle,[28] impaired myocardial perfusion,[14,39] inhibited myocardial contractility,[30] impaired myocardial oxygen consumption,[40] impaired left ventricular relaxation in pressure-overload hypertrophy,[41] enhanced cardiac afterload,[14,22,25-27] left ventricular remodeling in HF,[14,29,31,42,43] and further increase in myocardial damage.[14,25,27,28,31,38,43,44]

Experimental and clinical studies have provided new data about the mechanisms of specific aspects of endothelial function, therefore a potential mechanism of endothelial dysfunction is alteration of the signaling mechanisms involved in eNOS activation.[45]

Some novel approaches in patients with polymorphisms or mutations of genes that might play a pathogenic role in endothelial dysfunction investigate the relationship between genetic factors associated with endothelial function and the development of cardiac alterations.[45-48]

The ecNOS gene a/b polymorphism and the β-Nicotinamide adenine dinucleotide/nicotinamide adenine dinucleotide phosphate (NADH/NADPH) oxidase $p22^{phox}$ gene C242T polymorphism are found to be significantly associated with the development of CAD.[45,46] Regarding this topic, the following reduce NO bioavailability: polymorphisms in the eNOS gene,[47] upregulation of matrix metalloproteinase-2,49 and elevated levels of dimethylarginine, which is a competitive antagonist of endothelial nitric oxide synthase (eNOS). Some studies also found microRNA 217 upregulation, an NAD-dependent deacetylase, as responsible for endothelial alteration and eNOS activity decrease.[46-50]

Other factors that may also worsen endothelial function, such as activation of the endoplasmic

reticulum(ER) stress response,[41] high pro-inflammatory status, inflammatory cytokines, such as E-selectin and P-selectin,[52-55] over expression of tumor necrosis factor α, interleukin, high levels of plasminogen-activator inhibitor 1 (PAI-1),[56] increased adipose tissue mass, lower adropin levels[4] and lower tissue 5-methyltetrahydrofolate (5- MTHF)[56-57] levels, are correlated with endothelium-dependent vasodilation impairment.

Therefore, endothelial cycle dysfunction is influenced by several correlated mechanisms, which promote better the understanding of the topic and also improve its contribution in the cardiovascular field (Figure 2).

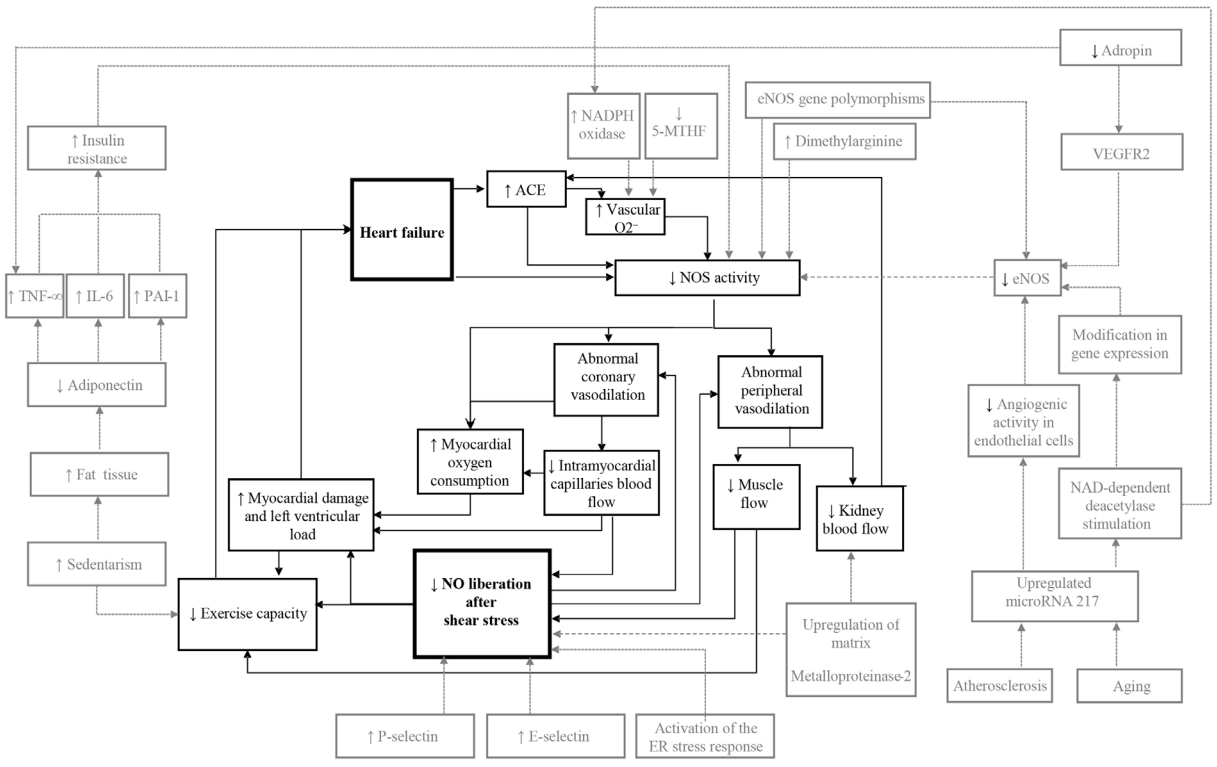

Figure 2 – *Representation of cycle dysfunction between heart failure and endothelial dysfunction with genetic and other influences*
↑ increase; ↓ decrease; 5- MTHF: 5-methyltetrahydrofolate; ACE: angiotensin converting enzyme; O2 - O2-radical; eNOS: endothelial nitric oxide synthase; ER: endoplasmic reticulum; IL-6: interleukin 6; NO: nitric oxide; PAI-1: plasminogen-activator inhibitor 1; TNF-∞: tumor necrosis factor α; VEGFR2: vascular endothelial growth factor receptor-2.

Conclusion

Low endothelial response to blood flow contributes to cardiac dysfunction. The other way around is also accurate, which involves cardiac dysfunction as a start for endothelial change. Therefore, a cycling dysfunction may be involved in both central and peripheral alterations.

Author contributions

Conception and design of the research: Tavares AC, Guimarães GV. Acquisition of data: Tavares AC, Guimarães GV. Analysis and interpretation of the data: Tavares AC, Bocchi EA. Writing of the manuscript: Tavares AC, Guimarães GV. Critical revision of the manuscript for intellectual content: Tavares AC, Bocchi EA, Guimarães GV. Making of Figures: Tavares AC.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

References

1. Brutsaert DL. Cardiac endothelial-myocardial signaling: its role in cardiac growth, contractile performance, and rhythmicity. Physiol Rev. 2003;83(1):59 –115.
2. Marti CN, Gheorghiade M, Kalogeropoulos AP, Georgiopoulou VV, Quyyumi AA, Butler J. Endothelial Dysfunction, Arterial Stiffness, and Heart Failure. J Am Coll Cardiol. 2012;60(16):1455–69
3. Mesquita ET. Socrates J. Rassi S. Villacorta H. Mady C. Insuficiência cardíaca com função sistólica preservada. Arquivos Brasileiros de Cardiologia. 2004; 82(4):494-500.
4. Verma S, Anderson TJ. Fundamentals of endothelial function for the clinical cardiologist. Circulation. 2002;105(5):546-9.
5. O'Rourke MF, Mancia G. Arterial stiffness. J Hypertens. 1999; 17(1):1–4.
6. Anderson TJ, Uehata A, Gerhard MD. Close relation of endothelial function in the human coronary and peripheral circulations. J Am Coll Cardiol. 1995;26(5):1235-41.
7. Pena AS, Wiltshire E, MacKenzie K, Gent R, Piotto L, Hirte C. Vascular endothelial and smooth muscle function relates to body mass index and glucose in obese and nonobese children. J Clin Endocrinol Metab. 2006;91(11):4467-71
8. Aggoun Y, Farpour-Lambert NJ, Marchand LM, Golay E, Maggio AB, Beghetti M. Impaired endothelial and smooth muscle functions and arterial stiffness appear before puberty in obese children and are associated with elevated ambulatory blood pressure. Eur Heart J. 2008;29(6):792-9.
9. Tavares AC, Bocchi EA, Guimarães GV (2012) Endothelial function in pre-pubertal children at risk of developing cardiomyopathy: a new frontier. Clinics. 2011;67(3):273–8.
10. Anderson TJ. Arterial stiffness or endothelial dysfunction as a surrogate marker of vascular risk. Can J Cardiol. 2006;22(Suppl B):72B-80B.
11. Carolyn SP, Lam MBBS, Dirk L, Brutsaert. Endothelial dysfunction. A pathophysiologic factor in heart failure with preserved ejection fraction.J Am Coll Cardiol. 2012;60(18):1787-9.
12. Widlansky ME, Gokce N, Keaney JF, Vita JA. The Clinical implications of endothelial dysfunction. J Am Coll Cardiol. 2003;42(7):1149–60.
13. Bauersachs J, Widder JD. Endothelial dysfunction in heart failure. Pharmacol Reports. 2008;60(1):119-26.
14. Maxwell AJ, Schauble E, Bernstein D, Cooke JP. Limb blood flow during exercise is dependent on nitric oxide. Circulation. 1998;98(4):369–74.
15. Nichols WW, Denardo SJ, Wilkinson IB, McEniery CM, Cockcroft J, O'Rourke MF. Effects of arterial stiffness, pulse wave velocity, and wave reflections on the central aortic pressure waveform. J Clin Hypertens. 2008;10(4): 295–303.
16. Akiyama E, Sugiyama S, Matsuzawa Y. Incremental prognostic significance of peripheral endothelial dysfunction in patients with heart failure with normal left ventricular ejection fraction. J Am Coll Cardiol. 2012;60(18):1778–86.
17. Fischer D, Rossa S, Landmesser U, Spiekermann S, Engberding N, Hornig B, et al. Endothelial dysfunction in patients with chronic heart failure is independently associated with increased incidence of hospitalization, cardiac transplantation, or death. Eur Heart J. 2005;26(1):65–9.
18. Nurnberger J, Keflioglu-Scheiber A, Opazo Saez AM, Wenzel RR, Philipp T, Schafers RF. Schafersa Augmentation index is associated with cardiovascular risk. J Hypertens. 2002,20(12):2407–.14
19. Laurent S, Cockcroft J. Bortel LV, Boutouyrie P, Giannattasio G, Hayoz D. Expert consensus document on arterial stiffness. Methodological issues and clinical applications. Eur Heart J. 2006;27(21):2588–605.
20. Dutra OP, Besser HW, Tridapalli H, Leiria TL, Afiune Neto A,Simão AF; Sociedade Brasileira de Cardiologia. II Brazilian guideline for severe hearat disease. Arq Bras Cardiol.2006;87(2):223-32.
21. Dod HS, Bhardwaj R, Sajja V, Weidner G, Hobbs GR, Konat GW, et al. Effect of Intensive Lifestyle Changes on Endothelial Function and on Inflammatory Markers of Atherosclerosis. J Cardiol. 2010;105(3):362–7.
22. Towbin JA. Lowe AM. Colan SD. Sleeper LA. Orav EJ. Clunie J. et. al. Incidence, causes, and outcomes of dilated cardiomyopathy in children. JAMA. 2006;296(15):1867-76.
23. Schachinger V, Britten MB, Zeiher AM. Prognostic impact of coronary vasodilator dysfunction on adverse long-term outcome of coronary heart disease, Circulation. 2000;101(16):1899–906.
24. Hambrecht R, Fiehn E, Weigl C, Gielen S, Hamann C, Kaiser R, et al. Regular physical exercise corrects endothelial dysfunction and improves exercise capacity in patients with chronic heart failure. Circulation. 1998;98(24):2709–15.
25. Buus NH, Bottcher M, Hermansen F, Sander M, Nielsen TT, Mulvany MJ Influence of nitric oxide synthase and adrenergic inhibition on adenosine-induced myocardial hyperemia. Circulation. 2001;104(19):2305–10.
26. Hornig B, Maier V, Drexler H. Physical training improves endothelial function in patients with chronic heart failure. Circulation. 1996;93(2):210–4.
27. Neglia D, Parodi O, Gallopin M, Sambuceti G, Giorgetti A, Pratali L, et al. Myocardial blood flow response to pacing tachycardia and to dipyridamole infusion in patients with dilated cardiomyopathy without overt heart failure. A quantitative assessment by positron emission tomography. Circulation. 1995;92(4):796–804.
28. Bassenge E. Endothelial function in different organs. Prog Cardiovasc Dis. 1996;39(3):209 –28.
29. Murohara T, Asahara T, Silver M, Bauters C, Masuda H, Kalka C, et al. Nitric oxide synthase modulates angiogenesis in response to tissue ischemia. J. Clin Invest. 1998;101(11):2567–78.
30. Mc Namara DM, Holubkov R, Postava L, Ramani R, Janosko K, Mathier M, et al. Effect of the Asp298 variant of endothelial nitric oxide synthase on survival for patients with congestive heart failure. Circulation. 2003;107(12):1598–602.
31. Jones SP, Greer JJM, van Haperen R, Duncker DJ, de Crom R, Lefer DJ. Endothelial nitric oxide synthase overexpression attenuates congestive heart failure in mice. Proc Natl Acad Sci USA. 2003; 100(8):4891–6.
32. Moncada S, Palmer RM, Higgs EA. Nitric oxide: physiology, pathophysiology, and pharmacology. Pharmacol Rev. 1991;43(2):109–42.
33. Boutouyrie P, Lacolley P, Girerd X, Beck L, Safar M, Laurent S. Sympathetic activation decreases medium-sized arterial compliance in humans. Am J Physiol. 1994;267(4 Pt 2):H1368-76.
34. Lepori M, Sartori C, Duplain H, Nicod P, Scherrer U. Interaction between cholinergic and nitrergic vasodilation: a novel mechanism of blood pressure control. Cardiovasc Res. 2001;51(4):767-72.
35. Rajagopalan S, Kurz S, Munzel T, Tarpey M, Freeman BA, Griendling KK, et al. Angiotensin IImediated hypertension in the rat increases vascular superoxide production via membrane NADH/NADPH oxidase activation. Contribution to alterations of vasomotor tone. J Clin Invest. 1996;97(8):1916–23.
36. Takeda Y, Miyamori I, Yoneda T, Hatakeyama H, Inaba S, Furukawa K, et al. Regulation of aldosterone synthase in human vascular endothelial cells by angiotensin II and adrenocorticotropin. J Clin Endocrinol Metab.1996;81(8):2797–800.
37. Farquharson CA, Struthers AD: Aldosterone induces acute endothelial dysfunction in vivo in humans: evidence for an aldosterone-induced vasculopathy. Clin Sci (Lond), 2002;103(4):425–31.
38. Giordano FJ, Gerber HP, Williams SP, Van Bruggen N, Bunting S, Ruiz-Lozano P, et al. A cardiac myocyte vascular endothelial growth factor paracrine pathway is required to maintain cardiac function. Proc Natl Acad Sci USA. 2001;98(10):5780–5.
39. Wilkinson IB, MacCallum H, Flint L, Cockcroft JR, Newby DE, Webb DJ. The influence of heart rate on augmentation index and central arterial pressure in humans. J Physiol. 2000;525(Pt 1):263-70.

40. Haywood GA, Tsao PS, von der Leyen HE, Mann MJ, Keeling PJ, Trindade PT, et al. Expression of inducible nitric oxide synthase in human heart failure. Circulation.1996;93(6):1087–94.

41. Ichiki T, Usui M, Kato M, Funakoshi Y, Ito K, Egashira K, et al. Downregulation of angiotensin II type 1 receptor gene transcription by nitric oxide. Hypertension. 1998;31(1 Pt 2) :342–8.

42. MacCarthy PA, Shah AM. Impaired endothelium-dependent regulation of ventricular relaxation in pressure-overload cardiac hypertrophy. Circulation. 2000;101(15):1854–60.

43. Hughes AD, Parker KH. Forward and backward waves in the arterial system: impedance or wave intensity analysis. Med Biol Eng Comput. 2009;47(2):207-10.

44. Scherrer–Crosbie M, Ullrich R, Bloch KD, Nakajima H, Nasseri B Aretz HT, et al. Endothelial nitric oxide synthase limits left ventricular remodeling after myocardial infarction in mice. Circulation. 2001;104(11):1286–91.

45. Lee WH, Hwang TH, Oh GT, Kwon SU, Choi YH, Park JE. Genetic factors associated with endothelial dysfunction affect the early onset of coronary artery disease in Korean males. Vasc Med. 2001;6(2):103-8.

46. da Silva CG, Specht A, Wegiel B, Ferran C, Kaczmarek E. Mechanism of purinergic activation of endothelial nitric oxide synthase in endothelial cells. Circulation. 2009;119(6):871–9.

47. Menghini R, Casagrande V, Cardellini M, Martelli E, Terrinoni A, Amati F, et al. MicroRNA 217 modulates endothelial cell senescence viasilent information regulator 1. Circulation. 2009;120(15):1524 –32.

48. Violi F, Sanguigni V, Carnevale R, Plebani A, Rossi P, Finocchi A, et al. Hereditary deficiency of gp91(phox) is associated with enhanced arterial dilatation: results of a multicenter study. Circulation. 2009;120(16): 1616-22.

49. Ray R, Shah AM. NADPH oxidase and endothelial cell function. Clin Sci (Lond). 2005 Sep;109(3):217-26.

50. Carvalho MHC, Colaço AL, Fortes, ZB. Citocinas, disfunção endotelial e resistência à Insulina. Arq Bras Endocrinol Metab. 2006;50(2):304-12.

51. Hummasti S, Hotamisligil GS. Endoplasmic reticulum stress and inflammation in obesity and diabetes. Circ Res. 2010;107(5):579 –91.

52. Ridker PM, Brown NJ, Vaughan DE, Harrison DG, Mehta JL. Established and emerging plasma biomarkers in the prediction of first atherothrombotic events. Circulation. 2004;109(29 Suppl 1):IV6-19.

53. Hwang SJ, Ballantyne CM, Sharrett AR, Smith LC, Davis CE, Gotto AM Jr, et al. Circulating adhesion molecules VCAM-1, ICAM-1, and E-selectin in carotid atherosclerosis and incident coronary heart disease cases: the Atherosclerosis Risk In Communities (ARIC) study. Circulation. 1997;96(12):4219-25.

54. Ridker PM, Hennekens CH, Roitman-Johnson B, Stampfer MJ, Allen J. Plasma concentration of soluble intercellular adhesion molecule 1 and risks of future myocardial infarction in apparently healthy men. Lancet. 1998;351(9096):88-92.

55. Vaughan DE. PAI-1 and atherothrombosis. J Thromb Haemost. 2005;3(8):1878-83.

56. Lovren F, Pan Y, Quan A, Singh KK, Shukla PC, Gupta M, et al. Adropin is a novel regulator of endothelial function. Circulation. 2010;122(11 Suppl):S185–S192.

57. Antoniades C, Shirodaria C, Leeson P, Baarholm OA, Van Assche T, Cunnington C, et al. MTHFR 677 C_T polymorphism reveals functional importance for 5-methyltetrahydrofolate, not homocysteine, in regulation of vascular redox state and endothelial function in human atherosclerosis. Circulation. 2009;119(18):2507–15.

International Journal of Cardiovascular Sciences. 2017;30(4):359-362

CASE REPORT

Cardiac Memory, an Underdiagnosed Condition

Margarida Oliveira, Olga Azevedo, Lucy Calvo, Bebiana Faria, Sílvia Ribeiro, António Lourenço

Hospital Senhora da Oliveira – Guimarães, Creixomil – Portugal

Introduction

Cardiac memory, also termed Chatterjee phenomenon, is a known yet uncommonly recognized entity in which myocardial repolarization is altered after abnormal ventricular activation, such as with artificial pacemakers, intermittent left bundle branch block, ventricular premature beats, ventricular pre-excitation or episodes of tachycardia.[1] This phenomenon is characterized by persistent but reversible T-wave changes on surface electrocardiogram (ECG) induced by an abnormal electrical activation pattern. The extent and direction of T-wave deviation depend on the duration and direction of abnormal electrical activation and can persist for several weeks. Rosenbaum et al.[2] found that the T-wave "resembled" the abnormal QRS vector. The pathophysiology underlying cardiac memory is still complex and evolving, but alterations in the transient outward potassium current — Ito1 — and changes in the phosphorylation status of the cAMP responsive element binding protein (CREB) have been reported.[3]

Although it seems that cardiac memory is a relatively benign pathophysiologic finding, it may lead to unnecessary and invasive diagnostic investigation if it is not recognized.

Here we report a patient presenting deep T-wave inversion after implantation of cardiac pacemaker.

Keywords

Electrocardiography; Pacemaker Artificial, Pre-Excitation, Mahaim; Myocardial Contraction/physiopathology.

Case report

We report the case of a 71-year-old woman with history of hypertension, hyperlipidemia and obesity admitted in the cardiology ward with syncope. ECG revealed advanced atrioventricular block and a narrow ventricular escape rhythm with a heart rate of 35 beats/minute, without evidence of ischemia or altered repolarization (Figure 1).

Transthoracic echocardiogram revealed normal left ventricular mass and function and no significant valve abnormalities. Metabolic causes for atrioventricular block were ruled out. Dual-chamber pacemaker was implanted without complications and she was discharged asymptomatic four days after admission.

She was followed up in cardiology consultation as well as pacemaker consultation for routine pacemaker interrogation. Four months after device implantation, pacemaker analysis revealed paroxysmal atrial fibrillation that was not previously known. Her 12-lead EKG revealed sinus rhythm and T wave inversion in leads DII, DIII and aVF and V3 to V6 (Figure 2).

The patient was completely asymptomatic and did not change any of her regular medication: lisinopril, atorvastatin, and omeprazole. Hypertension was medically controlled and cardiopulmonary and neurological tests were unremarkable. Transthoracic echocardiogram was repeated, revealing similar findings to the echocardiogram performed before pacemaker implantation, namely normal left ventricular mass and function, no valve abnormalities, no pericardial effusion and correct placement of pacemaker electrodes. She also underwent pharmacological stress echocardiogram, which proved negative to myocardial ischemia. Based on this clinical scenario, the final diagnosis of cardiac memory was assumed.

Mailing Address: Margarida Oliveira
Rua dos Cuteleiros, 114. Postal Code: 4835-044, Guimarães – Portugal
E-mail: margaridaramadaoliveira@gmail.com

DOI: 10.5935/2359-4802.20170048

Manuscript received November 01, 2016; revised manuscript January 31, 2017; accepted February 25, 2017.

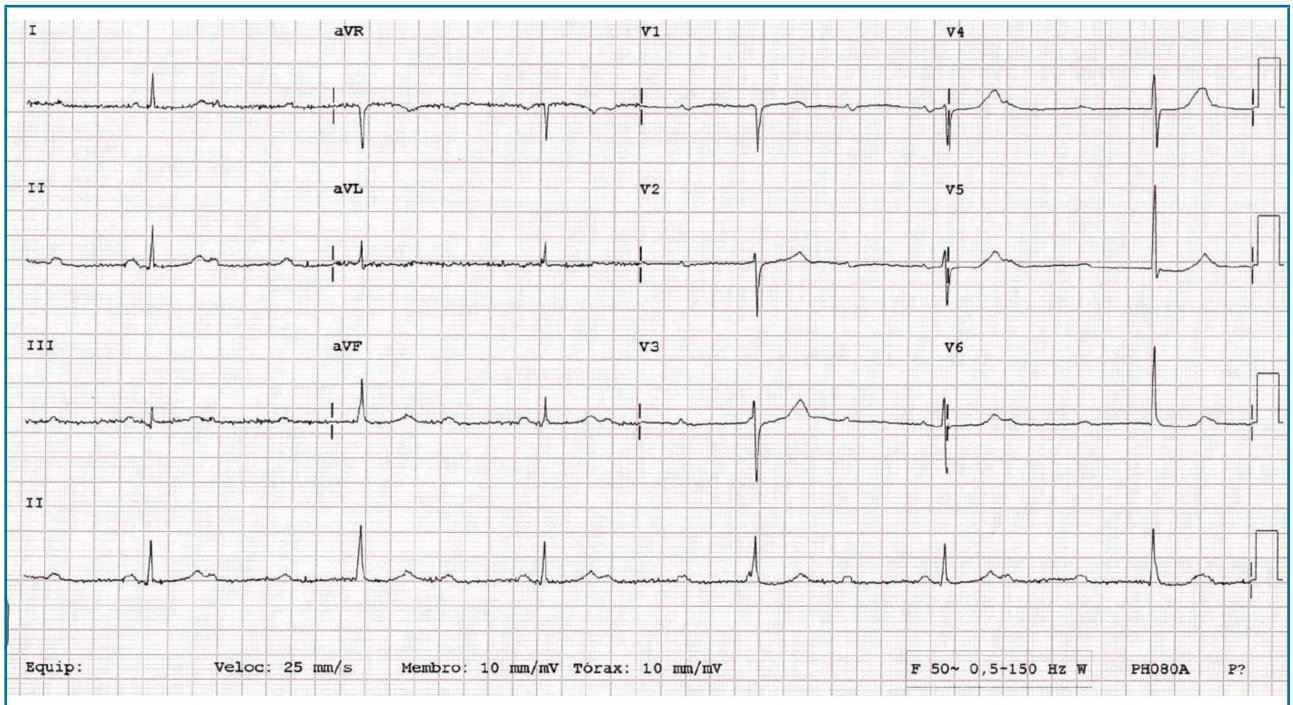

Figure 1 – *Electrocardiogram showing advanced atrioventricular block at hospital admission*

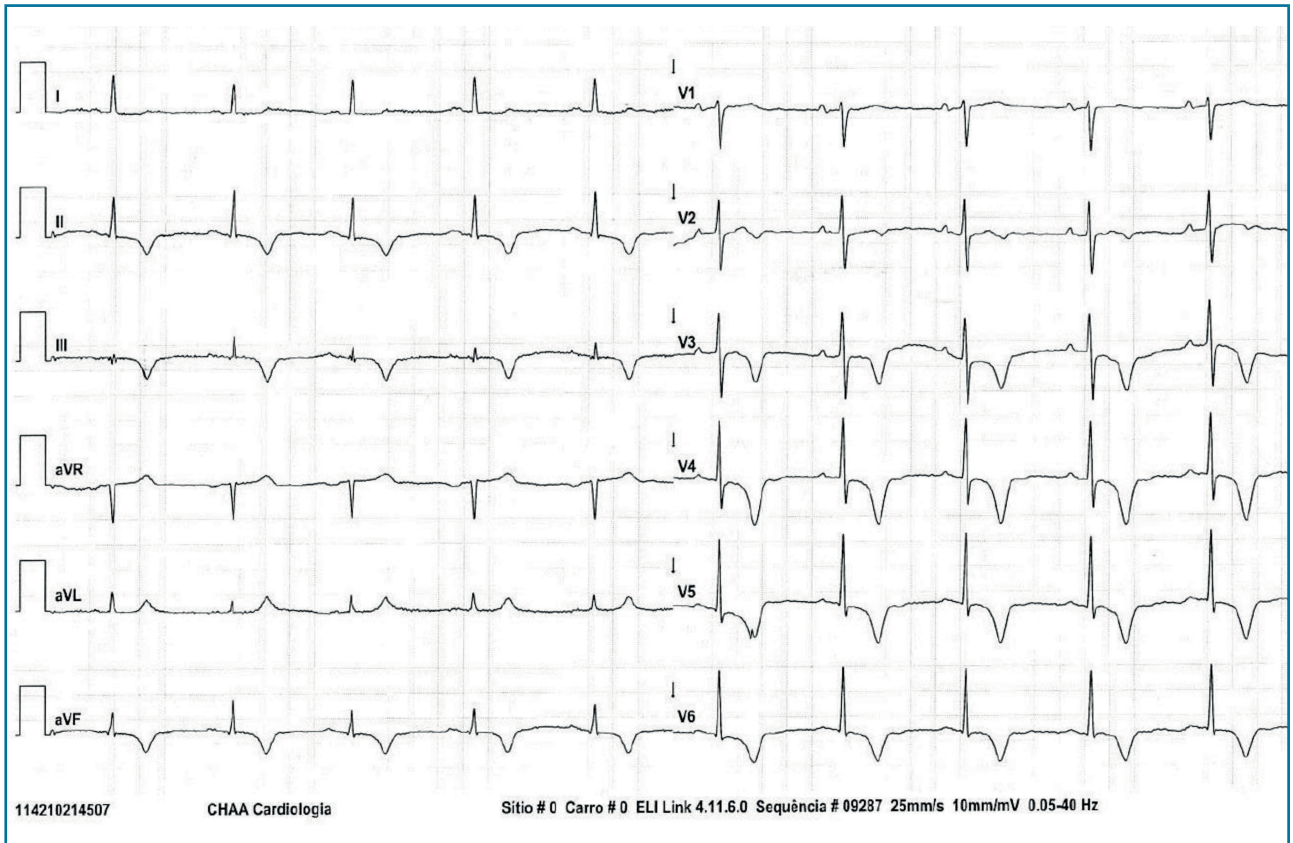

Figure 2 – *Electrocardiogram showing T-wave inversion in leads DII, DIII and aVF and V3 to V6 in the follow-up after pacemaker implantation*

Discussion

Cardiac memory is an underdiagnosed condition and physicians should be aware of this diagnosis to avoid unnecessary tests, hospital admissions and health costs. Our clinical case raises the awareness for this diagnosis among physicians.

Diagnosis of cardiac memory is based on defining the phenomenon itself. It is an exclusion diagnosis when a patient presents with new altered T-waves after a period of abnormal electrical activation and once we have ruled out other causes for repolarization changes. It is also reported that the combination of (a) positive T-wave in lead aVL, (b) positive or isoelectric T-wave in lead I, and (c) maximal voltage of T-wave inversion in precordial leads higher than in lead III has been shown to be associated to a sensitivity of 92% and a specificity of 100% for the diagnosis of cardiac memory.[4] It is also helpful, when possible, to document the normalization of repolarization changes.

Ruling out other causes for T-wave inversion is essential for the diagnosis of cardiac memory. There are several causes for T-wave inversion: myocardial ischemia, intracranial events, left ventricular hypertrophy, pericarditis, pulmonary embolus, myocardial contusion, mitral valve prolapse, myocarditis, apical septal hypertrophy, medications etc. Myocardial ischemia is one of the most serious and worrying diagnoses to be ruled out. It demands a careful and focused clinical history and an ischemia diagnostic test, in some cases, and even an invasive diagnostic method. It is also important to rule out intracranial bleeding by performing neurological tests and, when there are still doubts, computed tomography (CT) of the head. Echocardiogram can also help ruling out regional wall motion abnormalities, hypertrophy, mitral valve prolapse, pericardial fluid commonly present in pericarditis and cardiac repercussion of a significant pulmonary embolus. It is also important to review all medications taken by the patient, mainly antiarrhythmic drugs that can alter cardiac repolarization.

In our clinical case, clinical history and full physical examination, including neurological tests, allowed us to rule out several causes of new T-wave inversion, namely acute coronary syndrome, acute myocarditis, pulmonary embolism, stroke, status epilepticus or medications. Our patient also presented ECG clues, pointing towards the diagnosis of cardiac memory (Figure 2). Echocardiogram also allowed us to rule out several causes of T-wave inversion, such as left ventricular dysfunction, regional wall motion abnormalities due to myocardial infarct or myocarditis, left ventricular hypertrophy or pericardial effusion. Considering the patient age and the coexistence of cardiovascular risk factors, we decided to perform a pharmacological stress echocardiogram to rule out coronary heart disease. After a negative result in stress echocardiogram we assumed the diagnosis of cardiac memory.[4]

Cardiac memory was first recognized in 1940, but was named and studied in 1982 by Rosenbaum et al.[2] Electrophysiological remodeling following altered activation is characterized by distinct changes in the proximal (early-activated) versus distal (late-activated) areas from the site of altered activation. During ventricular activation, by artificial pacemaker, for example, there is a change in the action potential duration in the early (mild prolongation) and late (significant prolongation) activated myocardial areas. Consequently, regionally heterogeneous action potential remodeling occurs, which enhances regional repolarization gradients. This changes the repolarization vector direction that underlies the electrophysiological basis for T-wave memory(5). Several mechanisms have been proposed to underlie the development of cardiac memory: altered expression of transient outward potassium current, angiotensin II receptor-mediated signaling and, more recently, mechanical-strain-induced changes in action potential.

Despite early beliefs that cardiac memory was benign, some detrimental consequences of altered ventricular activation have been discussed, which include worsened mechanical function[5] and increased susceptibility to arrhythmias.[6] In addition, cardiac memory can also be responsible for patients being submitted to invasive diagnostic tests that put patients under unnecessary risks.

Pacing is an evolving area in cardiology and we are just starting to understand the pathophysiological consequences of the implantation of these devices. Cardiologists should definitely be aware of cardiac memory and be able to raise this suspicion whenever indicated, avoiding further unnecessary diagnostic workup.

Author contributions

Conception and design of the research: Oliveira M, Azevedo O, Ribeiro S. Acquisition of data: Oliveira M, Calvo L, Ribeiro S. Writing of the manuscript: Oliveira M, Calvo L, Faria B. Critical revision of the manuscript

for intellectual content: Azevedo O, Faria B, Ribeiro S, Lourenço A.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

References

1. Katz AM. T wave 'memory': possible causal relationship to stress-induced changes in cardiac ion channels? J Cardiovasc Eletrophysiol. 1992;3(2):150-9.
2. Rosenbaum MB, Blanco HH, Elizari MV, Lázzari JO, Davidenko JM. Eletrotonic modulation of the T wave and cardiac memory. Am J Cardiol. 1982;50(2):213-22.
3. Ozgen N, Rosen MR. Cardiac memory: a work in progress. Heart Rhythm. 2009;6(4):564-70.
4. Shvilkin A, Ho KK, Rosen MR, Josephson ME. T-vector direction differentiates postpacing from ischemic T-wave inversion in precordial leads. Circulation. 2005;111(8):969-74.
5. Jeyaraj D, Ashwath M, Rosenbaum DS. Pathophysiology and clinical implications of cardiac memory. Pacing Clin Electrophysiol. 2010;33(3):346-52.
6. Haverkamp W, Hordt M, Breithardt G, Borggrefe M. Torsade de pointes secondary to d,l-sotalol after catheter ablation of incessant atrioventricular reentrant tachycardia--evidence for a significant contribution of the "cardiac memory". Clin Cardiol. 1998;21:55-8.

International Journal of Cardiovascular Sciences. 2017;30(4):363-366

CASE REPORT

A Transcatheter Aortic Valve Implantation Without Aortography Guidance Due To Vascular Access Constraints Or Limitations

Oktay Ergene,[1] Hamza Duygu,[2] Volkan Emren,[3] Ugur Kocabas,[4] Levent Cerit[2]

Dokuz Eylül University,[1] Izmir, Turquia; Near East University,[2] Nicosia, Chipre; Afyon Kocatepe University School of Medicine,[3] Afyonkarahisar, Turquia; Ataturk Training and Research Hospital Department of Cardiology,[4] Izmir – Turquia

Introduction

Aortic valve replacement (AVR) is an established treatment modality in patients with severe symptomatic aortic stenosis (AS).[1,2] Given the increased mortality and morbidity of AVR for the high-risk patients and the poor long-term results of balloon aortic valvuloplasty, transcatheter aortic valve implantation (TAVI) is increasingly accepted treatment option who are not candidates for AVR.[3] We describe here a case of succesfully implanted Edwards SAPIEN XT transcatheter heart valve without aortography guidance due to multiple arterial access problems and complicated by iatrogenic De Bakey type III aortic dissection and severe paravalvular leak.

Case report

A 79-year-old woman was admitted with dyspnea (NYHA III) over a period of 3 months. She had a history of hypertension, diabetes mellitus, hyperlipidemia and chronic renal failure. A grade 3/6 systolic murmur was heard over the aortic area. Rhythm was sinus and electrocardiography fulfilled the criteria of left ventricular hypertrophy. Transthoracic echocardiography showed a severely calcified aortic stenosis with valve area of 0.6 cm^2, maximum gradient of 92 mmHg, mean gradient of 55 mmHg, left ventricular ejection fraction of 60%, aortic annular diameter of 20 mm, and ascending aorta of 35 mm.

Keywords

Transcatheter Aortic Valve Replacement; Dissection; Aortic Valve Stenosis.

Patient was evaluated by a heart team and deemed to be high risk for AVR (STS:12, euroscore:21) and accordingly decided to proceed to TAVI. Coronary angiography demonstrated the stenosis of LAD by 40%, first diagonal 40%, circumflex 85%, and proximal right coronary artery 50%. A mild to moderate aortic regurgitation was detected by aortography. The distance between left main coronary ostium (LMC) and aortic annulus was 11 mm. Right iliac artery was severly tortuous and no stenotic lesion was detected (Figure 1A, 1B).

We aimed to revascularize critical circumflex lesion before the procedure and percutaneous coronary intervention was performed. One month later, TAVI procedure scheduled. Under general anesthesia a left femoral cutdown was performed because of the severly tortuous right iliac artery. A pacemaker was placed from the right femoral vein. However, left Amplatz catheter over a Terumo and Exchange stiff wire was not got through to arcus aorta and an attemt to cross the aortic valve failed. Accordingly we noticed that the catheter was in the false aortic lumen extending from just below the left subclavian artery (Figure 1C). Soon after, catheter was completely removed and than left femoral artery repaired surgically. We were able to advance the pig-tail catheter to the ascending aorta to show the dissection by aortography via right femoral artery albeit severe tortuosity (Figure 1B, 1D). We decided to perform the TAVI procedure via right femoral artery despite of severe tortuosity. A pig-tail catheter, which is used to guide for the appropriate positioning of the prosthetic valve into aortic annulus thanks to aortography, couldn't moved due to bilateral severe brachial and subclavian artery tortuosity. Upon this, left main ostium and aortic annulus marked by a coloured pen on angiography screen

Mailing Adress: Levent Cerit
Near East University. Postal Code 07100, Nicosia – Chipre
E-mail: drcerit@hotmail.com, drcerit@yahoo.com

DOI: 10.5935/2359-4802.20170025

Manuscript received November 27, 2016, revised manuscript January 24, 2017, accepted January 24, 2017.

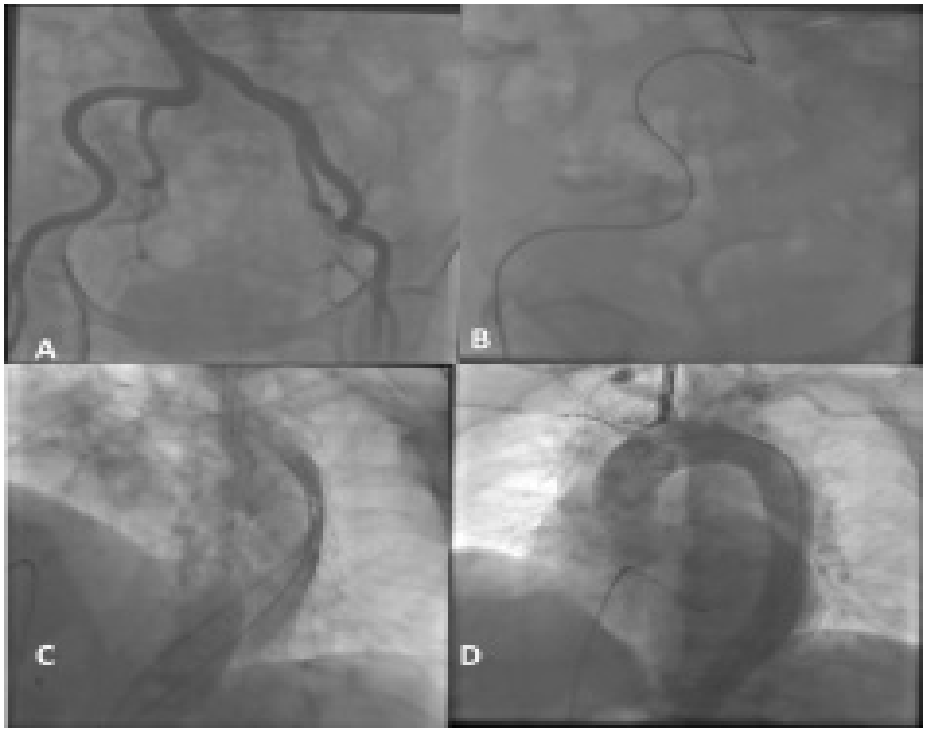

Figure 1 – *Angiographic images showing severe tortuous iliac artery (A. B), retrograd aortic dissection (C), and aortography via right femoral artery (D).*

accompanied by rapid ventricular pacing (Figure 2A). Immediately after, X-ray tube's angle and the patient left fixed positon, and prosthetic valve was started to implant without aortography. A 23 mm Edwards SAPIEN XT prosthetic aortic valve was deployed with rapid pacing at 180 bpm in accordance with this index drawings without aortography guidance (Figure 2B). But, aortogram following implantation showed severe paravalvular aortic regurgitation (Figure 2C). In order to solve this problem, prosthetic valve was crossed with AL-1 catheter and a straight and stiff wire, and successfully dilated with a 23 mm aortic balloon. Severe aortic regurgitation decreased to mild degree (Figure 2D). Transthorasic echocardiography obtained one day after the procedure revealed a dramatic decrease in aortic valve gradient (20/10 mmHg) and no aortic regurgitation. The patient was discharged from hospital on 6th postoperative day without any complication.

Discussion

TAVI is increasingly becoming an accepted option in the treatment of patients with severe symtomatic AS who are not eligible for surgery due to prohibitive risks and frailtiy.[4] Although TAVI is less invasive than conventional open heart surgery, it has several complications including the occlusion of coronary ostia, annular rupture, ventricular perforation, paravalvular regürgitation, heart block, device malposition or embolisation, stroke, major bleeding, vascular injury, and acute kidney injury.[4]

This case report highlightes how to cope with multiple complications during TAVI procedure. Dissection or perforation of the ilio-femoral arteries might occur in the presence of traumatic sheath insertion.[5] Dissection of the ascending or descending aorta might similarly occur due to catheter trauma or as an unpredictable complication of aortic valvuloplasty.[6] Nonocclusive retrograde dissections commonly heal once antegrade flow is restored; therefore limited dissections are often best managed conservatively as in our case.[5] Another issue is to place the valve into appropriate position. Due to arterial access problems we had to use only right femoral artery and we had no extra arterial access for aortography in order to show LMC ostium and aortic annulus. Upon this, first we

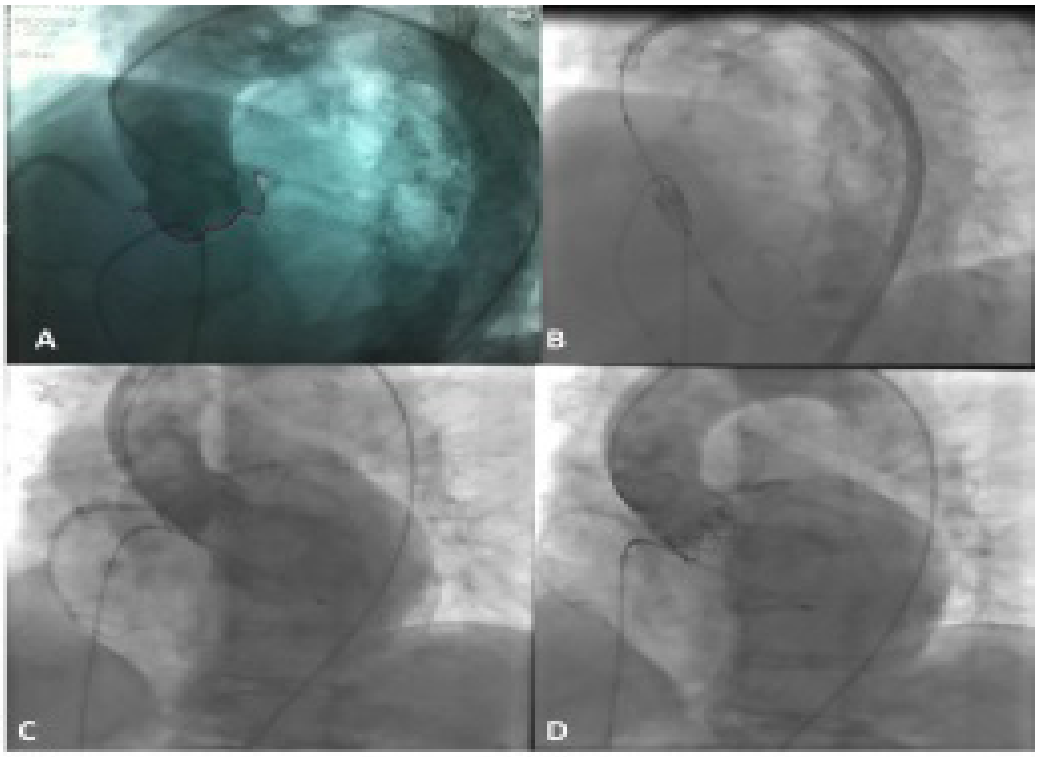

Figure 2 – *Deployment of prosthetic aortic valve based on index drawings (A, B), severe paravalvular aortic regurgitation following implantation (C), and aortogram showing mild regurgitation just after aortic balloon dilatation (D).*

marked the LMC ostium and aortic anulus on screen by a colourful pen during aortography accompanying with rapid pacing, then patient and X-ray tube fixed, and immediately after, the prosthesis valve implanted in accordance with this index drawing without aortography guidance. Another possible option could further define the annulus (landing zone) is to perform balloon aortic valvuloplasty (pre-dilatation) and to mark in the screen the waist and use it as a marker.

Mild or moderate aortic regurgitation can be seen after implantation. However hemodynamically severe post-procedural aortic regurgitation is rare.[4] These are generally caused by inadequate inflation of the balloon or by calcium deposits that prevent the valve unit to properly seat and seal within the annulus.[3,7,8] Severe paravalvular leak assuming incomplet expansion of prosthetic valve was declined dramatically after balloon dilatation in our patient.

Also in case of thoracoabdominal dissection a different second approach (transapical or transaortic) could be suggested. These approaches give the possibility to do the procedure with pig tail on the right femoral artery and more important avoid any contact with the new dissected fragile thoracoabdominal aorta / aortic arch and Novaflex system. Additionally, transesophageal echocardiography could have been used to position the valve.

In conclusion, this case demonstrates that maybe safe to implant percutaneous aortic valve with a single fixed contrast fluoro image after an acute major vascular complication occurred, and transradial approach is an important option during TAVI procedures and can also reduce the bleeding risks as a secondary vascular access site.

Author contributions

Conception and design of the research: Ergene O, Duygu H, Emren V, Kocabas U, Cerit L. Acquisition of data: Ergene O, Duygu H, Emren V, Kocabas U, Cerit L. Analysis and interpretation of the data: Ergene O, Duygu H, Kocabas U. Writing of the manuscript: Ergene O, Duygu H, Emren V, Kocabas U, Cerit L. Critical revision of the manuscript for intellectual content: Ergene O, Duygu H, Emren V, Kocabas U, Cerit L.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

References

1. Bonow RO, Carabello BA, Chatterjee K, de Leon AC Jr, Faxon DP, Freed MD, et al; American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revisethe 1998 Guidelines for the Management of Patients With Valvular Heart Disease). J Am Coll Cardiol. 2008; 52(13):e1-142.
2. Vahanian A, Baumgartner H, Bax J, Butchart E, Dion R, Filippatos G, et al; Task Force on the Management of Valvular Hearth Disease of the European Society of Cardiology.; ESC Committee for Practice Guidelines. Guidelines on the management of valvular heart disease: the Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology. Eur Heart J. 2007;28(2):230-68.
3. Webb JG, Pasupati S, Humphries K, Thompson C, Altwegg L, Moss R, et al. Percutaneous transarterial aortic valve replacement in selected high-risk patients with aortic stenosis. Circulation. 2007;116(7):755-63.
4. Holmes DR Jr, Mack MJ, Kaul S, Agnihotri A, Alexander KP, Bailey SR, et al. 2012 ACCF/AATS/SCAI/STS expert consensus document on transcatheter aortic valve replacement. J Am Coll Cardiol. 2012;59(13):1200-54.
5. Masson JB, Kovac J, Schuler G, Ye J, Cheung A, Kapadia S, et al. Transcatheter Aortic valve implantation: review of the nature, management, and avoidance of procedural complications. JACC Cardiovasc Interv. 2009;2(9):811-20.
6. Holmes DR Jr, Nishimura RA, Reeder GS. In-hospital mortality after balloon aortic valvuloplasty: frequency and associated factors. J Am Coll Cardiol. 1991;17(1):189-92.
7. Chiam PT, Ruiz CE. Percutaneous transcatheter aortic valve implantation: assessing results, judging outcomes, and planning trials: the interventionalist perspective. JACC Cardiovasc Interv. 2008;1(4):341-50.
8. Ong SH, Mueller R, Gerckens U. Iatrogenic dissection of the ascending aorta during TAVI sealed with the CoreValve revalving prosthesis. Catheter Cardiovasc Interv. 2011;77(6):910-4.