

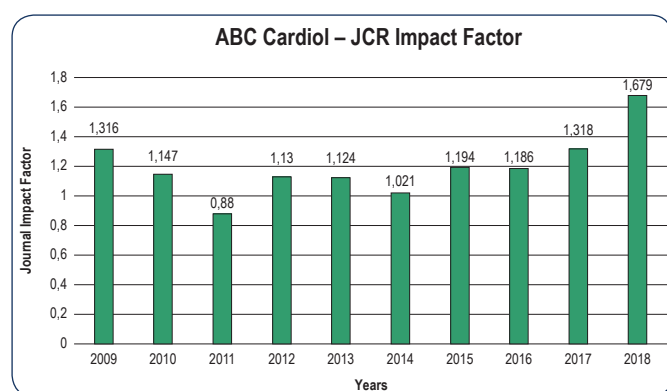


Figure 1 da Page 06.

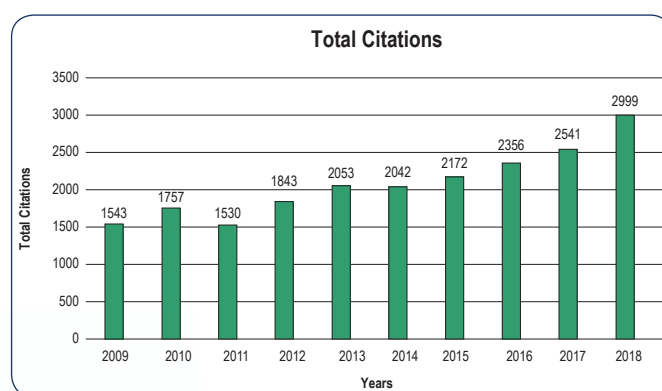


Figure 2 da Page 06.

Chief Editor

Carlos Rochitte

Internacional Coeditor

João Lima

Editors

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

ABC Cardiol IF – 1.679 – A new historical record

Characterization of decellularized pericardium

Risks scores in acute coronary syndromes

Sirtuins in acute myocardial infarction patients

Readmission of patients with coronary syndrome

Dietary patterns and adiposity in children

The profile of the brazilian cardiologist

Mean platelet volume, coronary artery fistula

A novel mutation in Fabry disease

ECG/VCG in the current clinical practice

Contents

Editorial

Just-Released JCR Impact Factor Shows Strong and Steady Increase for ABC Cardiol – 1.679 - A New Historical Record

Carlos E. Rochitte

.....page 1

Editorial

Heart Failure Awareness Day: A Tribute to the Genius Carlos Chagas

Evandro Tinoco Mesquita, Aurea Lucia Alves de Azevedo Grippa de Souza, Salvador Rassi

.....page 5

Editorial

Non-Pharmacological Treatment of Cardiovascular Disease | Importance of Physical Exercise

Mariana Janini Gomes, Luana Urbano Pagan, Marina Politi Okoshi

.....page 9

Original Article

Characterization of Decellularized Human Pericardium for Tissue Engineering and Regenerative Medicine Applications

Luciana Wollmann, Paula Suss, João Mendonça, Cesar Luzia, Andressa Schittini, George Willian Xavier da Rosa, Francisco Costa, Felipe F. Tuon

.....page 11

Short Editorial

Decellularization of Human Pericardium with Potential Application in Regenerative Medicine

Estela de Oliveira Lima, Adriana Camargo Ferrasi, Andreas Kaasi

.....page 18

Original Article

Application of Risks Scores in Acute Coronary Syndromes. How Does ProACS Hold Up Against Other Risks Scores?

Júlio Gil, Luís Abreu, Hugo Antunes, Maria Luísa Gonçalves, Maria Inês Pires, Luís Ferreira dos Santos, Carla Henriques, Ana Matos, José Costa Cabral, Jorge Oliveira Santos

.....page 20

Short Editorial

Is ProACS Score Just another Risk Stratification Score, or is it Ready for Implementation in Clinical Practice?

Ana Teresa Timóteo

.....page 31

Original Article

Serum Sirtuin 1, 3 and 6 Levels in Acute Myocardial Infarction Patients

Emrullah Kızıltunç, Arzu Kösem, Can Özkan, Burcu Uğurlu Ilgin, Harun Kundi, Mustafa Çetin, Ender Ornek

.....page 33

Short Editorial

Biomarkers in Acute Myocardial Infarction Diagnosis and Prognosis

Paula F. Martinez, Silvio A. Oliveira Jr. Bertha F. Pologato, Katashi Okoshi, Marina P. Okoshi

.....page 40

Original Article

Readmission of Patients with Acute Coronary Syndrome and Determinants

Larissa Marina Santana Mendonça de Oliveira, Ingrid Maria Novais Barros de Carvalho Costa, Danielle Góes da Silva, José Rodrigo Santos Santos Silva, José Augusto Soares Barreto-Filho, Marcos Antônio Almeida-Santos, Joselina Luzia Meneses Oliveira, Mirella Dornelas Batalha Moreira Buarque, Diva Aliete dos Santos Vieira, Antônio Carlos Sobral Sousa

.....page 42

Short Editorial

Hospital Readmissions after Acute Coronary Syndromes

Alfredo J. Mansur

.....page 50

Original Article

Association of Dietary Patterns with Excess Weight and Body Adiposity in Brazilian Children: The Pase-Brasil Study

Naruna Pereira Rocha, Luana Cupertino Milagres, Mariana De Santis Filgueiras, Lara Gomes Suhett, Mariane Alves Silva, Fernanda Martins de Albuquerque, Andréia Queiroz Ribeiro, Sarah Aparecida Vieira, Juliana Farias de Novaes

.....page 52

Short Editorial

Dietary Patterns and Healthy Habits Along the Life Course

Lucia Campos Pellanda

.....page 60

Original Article

The Profile of the Brazilian Cardiologist – A Sample of Members of the Brazilian Society of Cardiology

Lucas Simonetto Faganello, Mauricio Pimentel, Carisi Anne Polanczyk, Tiago Zimerman, Marcus Vinicius Bolivar Malachias, Oscar Pereira Dutra, Leandro Ioschpe Zimerman

.....page 62

Short Editorial

Profile of Brazilian Cardiologists: An Overview of Female Leadership in Cardiology and Stress — Challenges for the Next Decade

Evandro Tinoco Mesquita, Eduardo Thadeu de Oliveira Correia, Letícia Mara dos Santos Barbeta
.....page 69

Original Article

Does Mean Platelet Volume Decrease in the presence of Coronary Artery Fistula?

Isa Sincer, Yusuf Çekici, Mehmet Cosgun, Gulali Aktas, Yilmaz Gunes, Emrah Erdal, Asli Kurtar Mansiroglu, Mehmet Inanir
.....page 71

Original Article

GLA Gene Mutation in Hypertrophic Cardiomyopathy with a New Variant Description: Is it Fabry's Disease?

Ândrea Virgínia Chaves-Markman, Manuel Markman, Eveline Barros Calado, Ricardo Flores Pires, Marcelo Antônio Oliveira Santos-Veloso, Catarina Maria Fonseca Pereira, Andréa Bezerra de Melo da Silveira Lordsleem, Sandro Gonçalves de Lima, Brivaldo Markman Filho, Dinaldo Cavalcanti de Oliveira
.....page 77

Short Editorial

Description of a New GLA Gene Variant in a Patient with Hypertrophic Cardiomyopathy. Is it Fabry Disease?

Marcelo Imbroinise Bittencourt
.....page 85

Review Article

Applicability of the Electro-Vectorcardiogram in Current Clinical Practice

Carlos Alberto Pastore, Nelson Samesima, Horacio Gomes Pereira Filho, Nancy Maria Martins de Oliveira Tobias, Bruna Affonso Madaloso, Mirella Esmahotto Facin
.....page 87

Viewpoint

Telemedicine and the Doctor/Patient Relationship

Protásio Lemos da Luz
.....page 100

Clinicoradiological Session

Case 4/2019 – Pulmonary Atresia, Ventricular Septal Defect, and Systemic-Pulmonary Collateral Circulation developing after prior Blalock-Taussig, in a Symptomatic 47-Year-Old Adult

Edmar Atik, Maria Angélica Binotto, Alessandra Costa Barreto, Walther Ishikawa
.....page 103

Case Report

Vasospasm during Exertion: New Pathophysiological Insights

Gonzalo Navarrete, Eduardo Pozo, Fernando Rivero, Teresa Bastante, Luis Jesús Jiménez-Borreguero, Fernando Alfonso
.....page 106

Letter to the Editor

Prolonged PR Interval and Outcome in Cardiac Resynchronization Therapy

Jakrin Kewcharoen e Chanavuth Kanitsoraphan

.....page 109

Statement

Statement on Antiplatelet Agents and Anticoagulants in Cardiology – 2019

Carlos V. Serrano Jr., Alexandre de M. Soeiro, Tatiana C. A. Torres Leal, Lucas C. Godoy,¹ Bruno Biselli, Luiz Akira Hata, Eduardo B. Martins, Isabela C. K. Abud-Manta, Caio A. M. Tavares, Francisco Akira Malta Cardozo, Múcio Tavares de Oliveira Jr.

.....page 111

Statement

Position Statement on Indications of Echocardiography in Adults – 2019

Silvio Henrique Barberato, Minna Moreira Dias Romano, Adenalva Lima de Souza Beck, Ana Clara Tude Rodrigues, André Luiz Cerqueira de Almeida, Bruna Morhy Borges Leal Assunção, Eliza de Almeida Gripp, Fabio Villaça Guimarães Filho, Henry Abensur, José Maria Del Castillo, Marcelo Haertel Miglioranza, Marcelo Luiz Campos Vieira, Márcio Vinicius Lins de Barros, Maria do Carmo Pereira Nunes, Maria Estefania Bosco Otto, Renato de Aguiar Horteagal, Rodrigo Bellio de Mattos Barretto, Thais Harada Campos, Vicente Nicoliello de Siqueira, Samira Saady Morhy

.....page 135

Erratum

.....page 182



ABC Cardiol

Journal of Brazilian Society of Cardiology

JOURNAL OF BRAZILIAN SOCIETY OF CARDIOLOGY - Published since 1943

Scientific Director

Dalton Bertolim Prêcoma

Chief Editor

Carlos Eduardo Rochitte

Internacional Coeditor

João Lima

Associated Editors

Clinical Cardiology

Gláucia Maria Moraes
de Oliveira

Surgical Cardiology

Alexandre Siciliano
Colafranceschi

Interventionist Cardiology

Pedro A. Lemos

Pediatric/Congenital Cardiology

Ieda Biscegli Jatene
Vitor C. Guerra

Arrhythmias/Pacemaker

Mauricio Scanavacca

Non-Invasive Diagnostic Methods

João Luiz Cavalcante

Basic or Experimental Research

Marina Politi Okoshi

Epidemiology/Statistics

Marcio Sommer Bittencourt

Arterial Hypertension

Paulo Cesar B. V. Jardim

Ergometrics, Exercise and Cardiac Rehabilitation

Ricardo Stein

First Editor (1948-1953)

† Jairo Ramos

Editorial Board

Brazil

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Exterior

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

Alan Maisel – Long Island University, Nova York – USA

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

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

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

Ana Teresa Timóteo – Hospital Santa Marta, Lisboa – Portugal

Cândida Fonseca – Universidade Nova de Lisboa, Lisboa – Portugal

Fausto Pinto – Universidade de Lisboa, Lisboa – Portugal

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

James de Lemos – Parkland Memorial Hospital, Texas – USA

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

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

Jorge Ferreira – Hospital de Santa Cruz, Carnaxide – Portugal

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

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

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

Maria Pilar Tornos – Hospital Quirónsalud Barcelona, Barcelona – Spain

Nuno Bettencourt – Universidade do Porto, Porto – Portugal

Pedro Brugada – Universiteit Brussel, Brussels – Belgium

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

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

Piero Anversa – University of Parma, Parma – Italy

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

Sociedade Brasileira de Cardiologia

President

Oscar Pereira Dutra

Vice-President

José Wanderley Neto

President-elect

Marcelo Queiroga

Scientific Director

Dalton Bertolim Prêcoma

Financial Director

Denilson Campos de Albuquerque

Administrative Director

Wolney de Andrade Martins

Government Liaison Director

José Carlos Quinaglia e Silva

Information Technology Director

Miguel Antônio Moretti

Communication Director

Romeu Sergio Meneghelo

Research Director

Fernando Bacal

Assistance Quality Director

Evandro Tinoco Mesquita

Specialized Departments Director

Audes Diógenes de Magalhães Feitosa

State and Regional Relations Director

Weimar Kunz Sebba Barroso de Souza

Cardiovascular Health Promotion Director - SBC/Funcor

Fernando Augusto Alves da Costa

Chief Editor of the Arquivos Brasileiros de Cardiologia

Carlos Eduardo Rochitte

Chief Editor of the International Journal of Cardiovascular Sciences

Claudio Tinoco Mesquita

Presidents of State and Regional Brazilian Societies of Cardiology:

SBC/AL – Edvaldo Ferreira Xavier Júnior

SBC/AM – João Marcos Bemfica Barbosa Ferreira

SBC/BA – Emerson Costa Porto

SBC/CE – Maria Tereza Sá Leitão Ramos Borges

SBC/DF – Ederaldo Brandão Leite

SBC/ES – Fatima Cristina Monteiro Pedroti

SBC/GO – Gilson Cassem Ramos

SBC/MA – Aldryn Nunes Castro

SBC/MG – Carlos Eduardo de Souza Miranda

SBC/MS – Christiano Henrique Souza Pereira

SBC/MT – Roberto Candia

SBC/NNE – Maria Alayde Mendonca da Silva

SBC/PA – Moacyr Magno Palmeira

SBC/PB – Fátima Elizabeth Fonseca de
Oliveira Negri

SBC/PE – Audes Diógenes de Magalhães Feitosa

SBC/PI – Luiza Magna de Sá Cardoso
Jung Batista

SBC/PR – João Vicente Vitola

SBC/RN – Sebastião Vieira de Freitas Filho

SBC/SC – Wálmore Pereira de Siqueira Junior

SBC/SE – Sheyla Cristina Tonheiro Ferro da Silva

SBC/TO – Wallace André Pedro da Silva

SOCERGS – Daniel Souto Silveira

SOCERJ – Andréa Araujo Brandão

SOCERON – Fernanda Dettmann

SOCESP – José Francisco Kerr Saraiva

Presidents of the Specialized Departaments and Study Groups

SBC/DA – Maria Cristina de Oliveira Izar

SBC/DCC – João Luiz Fernandes Petriz

SBC/DCC/CP – Andressa Mussi Soares

SBC/DCM – Marildes Luiza de Castro

SBC/DECAGE – Elizabeth da Rosa Duarte

SBC/DEIC – Salvador Rassi

SBC/DERC – Tales de Carvalho

SBC/DFCVR – Antoinette Oliveira Blackman

SBC/DHA – Rui Manuel dos Santos Pova

SBC/DIC – Marcelo Luiz Campos Vieira

SBCCV – Rui Manuel de Sousa S. Antunes
de Almeida

SOBRAC – Jose Carlos Moura Jorge

SBHCI – Viviana de Mello Guzzo Lemke

DCC/GAPO – Pedro Silvio Farsky

DERC/GECESP – Antonio Carlos Avanza Jr

DERC/GEEN – Rafael Willain Lopes

DERC/GERCPM – Mauricio Milani

DCC/GECEI – Luiz Bezerra Neto

DCC/GECEI – Roberto Kalil Filho

DEIC/GEICPED – Estela Azeka

DCC/GEMCA – Roberto Esporcatte

DEIC/GEMIC – Fabio Fernandes

DCC/GERTC – Juliano de Lara Fernandes

DEIC/GETAC – Silvia Moreira Ayub Ferreira

Arquivos Brasileiros de Cardiologia

Volume 113, Nº 1, July 2019

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



Address: Av. Marechal Câmara, 160 - 3º andar - Sala 330
20020-907 • Centro • Rio de Janeiro, RJ • Brasil

Phone.: (21) 3478-2700

E-mail: arquivos@cardiol.br

www.arquivosonline.com.br

SciELO: www.scielo.br

Commercial Department

Phone: (11) 3411-5500

E-mail: comerciaisp@cardiol.br

Editorial Production

SBC - Internal Publication Department

Graphic Design and Diagramming

Graphic Design

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

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

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



Affiliated at the Brazilian
Medical Association

SUPPORT



Ministério da
Educação

Ministério da
Ciência e Tecnologia



Just-Released JCR Impact Factor Shows Strong and Steady Increase for ABC Cardiol – 1.679 - A New Historical Record

Carlos E. Rochitte*^{1B}

Instituto do Coração - Incor, São Paulo, SP – Brazil

* Editor-Chefe da ABC Cardiol – Arquivos Brasileiros de Cardiologia

Dear friends from the Cardiology and Cardiovascular scientific community in Brazil and abroad, please allow me this short editorial with extraordinary news on the ABC Cardiol Journal, accompanied by data, of course.

We are delighted to announce that our peer-reviewed journal of The Brazilian Society of Cardiology, the ABC Cardiol (Arquivos Brasileiros de Cardiologia), has seen significant increase in its impact factor rating in the latest Journal of Citation Reports (JCR) release. Our impact factor went up from 1.318, released last year (2017 rate) to 1.679 this year (2018 rate), a 27% increase in one year and the highest impact factor ever for ABC Cardiol.

We can see a clear and steep increase of the impact factor in Figure 1,¹ breaking the barrier of 1,5 impact factor. Articles published in the ABC Cardiol received a staggering 3000 citations in 2018 alone (Figure 2).¹ Another barrier that was broken by ABC Cardiol this year is the third Quartile. We are now ranked at the Q3 of all 136 Cardiac and Cardiovascular System journals in the World (Table 1).¹ ABC Cardiol galvanized his position of the highest ranked Journal in Cardiology and Cardiovascular Science in Latin America, position that was reached and maintained since 2014 (see Table 2).²

One important aspect of the progression of our JCR impact factor is depicted in the Table 3.¹ While in the same period of 2017 to 2018, most of Cardiology and Cardiovascular Science and Medical Journals in Brazil only maintained or even decreased their impact factor, ABC Cardiol steadily increased in a significantly amount its impact factor, only followed by a basic research journal. So, in our scientific community in Latin America ABC Cardiol has established itself as the main reference journal for Cardiology and Cardiovascular Science.

The rise in impact factor means that our research community is recognizing the articles being accepted and

published in ABC Cardiol journal as relevant and impactful science. This accomplishment fulfills ABC Cardiol mission that is to promote new knowledge and publish the latest research, emerging technologies and breakthrough advances in Cardiology and cardiac diseases.

ABC Cardiol journal is free and open access journal that can be viewed, downloaded and accessed by mobile app from anywhere in the World. The readers can interact with editorial board members and authors through social media (Facebook, Tweeter, Instagram, etc) and through movie posts in our newly re-designed web-portal.

This important step on the ABC Cardiol progression toward a higher scientific rank was only possible by a continuous editorial policy that started several years back with Dr. Luis Felipe Moreira, former Editor-in-Chief, to whom we are deeply grateful. Our international and talented associate editors' team, dedicated editorial board and reviewers are by far the main reason that led ABC Cardiol to his current position. The strong support from our Brazilian Society of Cardiology board of directors to the ABC Cardiol has been crucial to achieve our goals of increasing our impact and presence in the scientific community. Our dedicated team of editorial assistants that does not measure the efforts to achieve timely and high quality publication is of paramount importance to our ABC Cardiol journal operation. For me as editor-in-chief, running ABC Cardiol and working together with this great team of professionals in our office in São Paulo and in Rio de Janeiro has been a blessing. Thank you so much for this delightful experience.

Our editorial policy is focused in the scientific quality of submitted manuscripts and the novelty they bring to the field. We welcome new and revolutionary ideas brought to light by rigorous scientific method in well-written manuscripts. Our main language is English, but we accept and publish all articles bilingually, English and Portuguese.

We have editorial comments for all published original articles, which place the new science in context with the specific research field. ABC Cardiol is also the home of all clinical guidelines, statements and expert consensus endorsed by the Brazilian Society of Cardiology. All guidelines are now published in Portuguese and English and within the body of the Journal. With these recent improvements in our editorial policy and continuous support from our scientific community and post-graduation programs in Brazil we hope we can break another impact factor barrier next year. Thank you all very much.

Keywords

Bibliometrics; Journal Impact Factor; Periodicals as Topic; Scimago.

Mailing Address: Carlos E. Rochitte •

Av. Dr. Enéas de Carvalho Aguiar 44 - Andar AB - Ressonância & Tomografia

- Cerqueira César - 05403-000 - São Paulo, SP – Brazil

E-mail: rochitte@cardiol.br, rochitte@incor.usp.br

DOI: 10.5935/abc.20190135

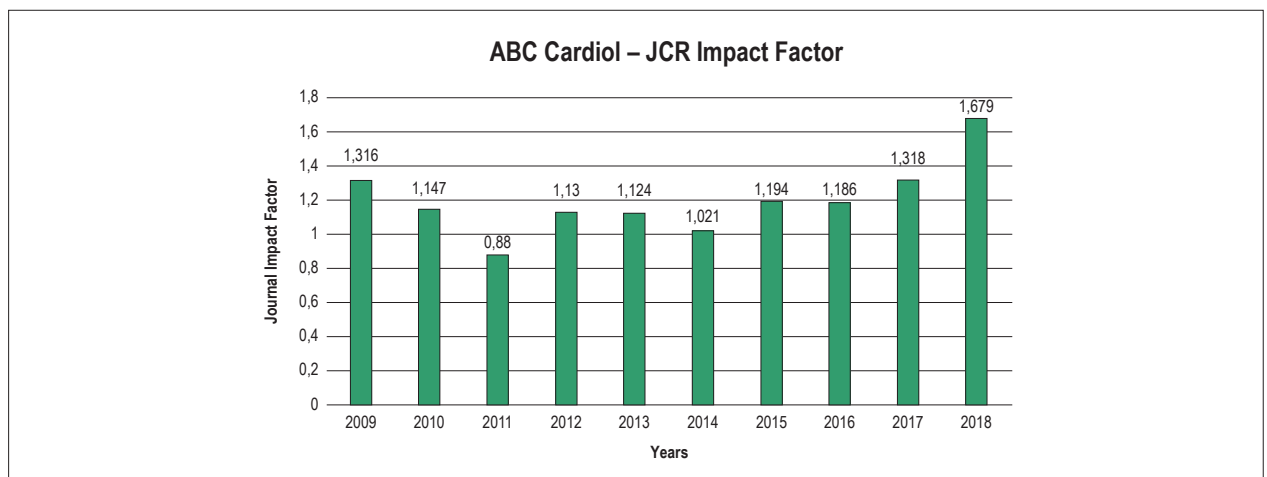


Figure 1 – ABC Cardiol JCR Impact Factor from 2009 to 2018. Source: JCR¹

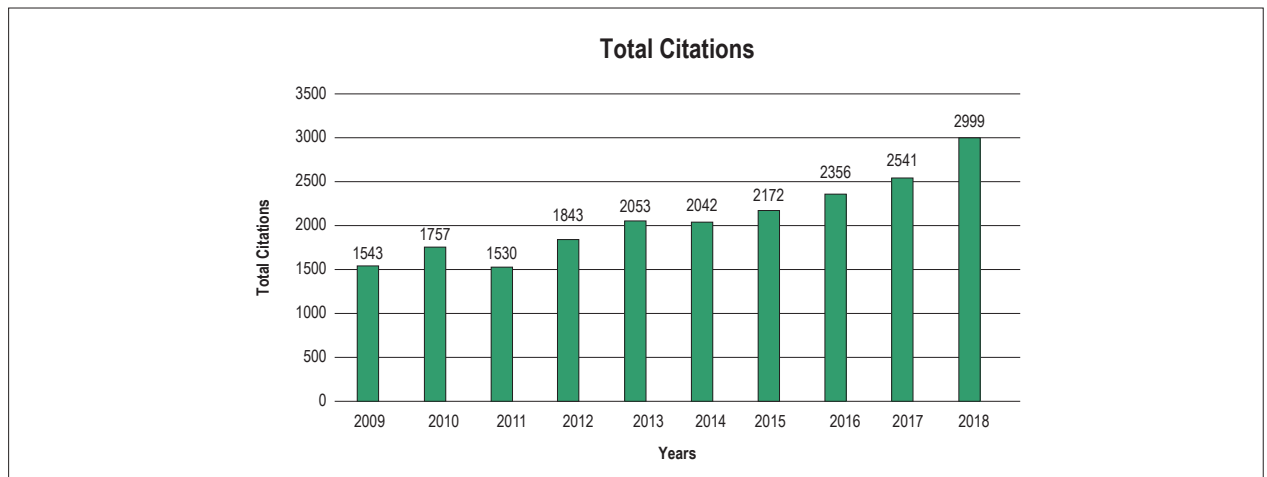


Figure 2 – ABC Cardiol Total Citations per Year. Source JCR¹

Table 1 – ABC Cardiol Quartiles Rank from 2009 to 2018. Source JCR¹

JCR year	Cardiac and Cardiovascular systems		
	Rank	Quartile	JIF Percentile
2018	98/136	Q3	23.309
2017	106/128	Q4	17.578
2016	107/126	Q4	15.476
2015	97/124	Q4	22.177
2014	100/123	Q4	19.106
2013	96/125	Q4	23.600
2012	91/124	Q3	27.016
2011	98/117	Q4	16.667
2010	87/114	Q4	24.123
2009	63/95	Q3	34.211

Table 2 – Rank in Cardiology and Cardiovascular Science Journals in Latin America. Source SCIMAGO²

Rank	Title	SJR	SJR Quartile	H index	Total Docs. (2018)	Total Docs. (3years)	Total Refs.	Total Cites (3years)	Citable Docs. (3years)	Cites / Doc. (2years)	Ref./Doc.	Country
1	Arquivos Brasileiros de Cardiologia	0,407	Q3	45	250	595	5472	592	418	1,41	21,89	Brazil
2	Brazilian Journal of Cardiovascular Surgery	0,324	Q3	22	109	290	2058	234	237	0,83	18,88	Brazil
3	Jornal Vascular Brasileiro	0,158	Q4	13	61	178	1146	71	162	0,42	18,79	Brazil
4	Archivos de Cardiologia de Mexico	0,142	Q4	16	94	195	2043	46	174	0,26	21,73	Mexico
5	Revista Argentina de Cardiologia	0,127	Q4	9	109	368	1375	18	159	0,1	12,61	Argentina
6	Revista Latinoamericana de Hipertension	0,124	Q4	5	95	53	3091	25	53	0,55	32,54	Venezuela
7	Revista Colombiana de Cardiologia	0,117	Q4	8	135	411	3196	54	386	0,12	23,67	Colombia
8	Revista Brasileira de Cardiologia Invasiva	0,113	Q4	7	0	100	0	5	81	0	0	Brazil
9	Revista de la Federacion Argentina de Cardiologia	0,112	Q4	4	30	158	449	9	124	0,04	14,97	Argentina
10	Revista Mexicana de Angiologia	0,112	Q4	3	23	74	288	3	62	0,05	12,52	Mexico
11	Insuficiencia Cardiaca	0,109	Q4	5	21	77	592	3	67	0,02	28,19	Argentina
12	Revista Mexicana de Cardiologia	0,104	Q4	4	22	94	638	10	86	0,09	29	Mexico
13	Revista Mexicana de Enfermeria Cardiologica	0,101	Q4	2	0	29	0	0	24	0	0	Mexico

Table 3 – JCR impact factor for 2017 and 2018 for Brazilian Journals (Cardiovascular Field, Medicine and Basic Research). Source JCR¹

Journal	Impact Factor 2017	Impact Factor 2018
Arquivos Brasileiros de Cardiologia	1,318	1,679
Brazilian Journal of Cardiovascular Surgery	0,805	0,796
Brazilian Journal of Medical and Biological Research	1,492	1,850
Clinics	1,245	1,127
Memorias do Instituto Oswaldo Cruz	2,833	2,368
Revista da Associacao Medica Brasileira	0,736	0,801
Sao Paulo Medical Journal	1,063	1,088

References

1. Journal Citation Reports. Clarivate Analytics. [Cited in 2019 June]. Available from: <https://jcr-clarivate.ez67.periodicos.capes.gov.br/JCRJournalHomeAction.action>
2. Scimago Journal & Country Rank. Scimago Lab.[Cited in 2019 June 29]. Available from: <https://www.scimagojr.com>



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

Heart Failure Awareness Day: A Tribute to the Genius Carlos Chagas

Evandro Tinoco Mesquita,^{1,2,3} Aurea Lucia Alves de Azevedo Grippa de Souza,¹ Salvador Rassi^{4,5}

Universidade Federal Fluminense,¹ Niterói, RJ – Brazil

Hospital Pró-Cardíaco,² Rio de Janeiro, RJ – Brazil

Departamento de Insuficiência Cardíaca da Sociedade Brasileira de Cardiologia (DEIC/SBC) - Diretoria Científica,³ Rio de Janeiro, RJ – Brazil

Universidade Federal de Goiás,⁴ Goiânia, GO – Brazil

Departamento de Insuficiência Cardíaca da Sociedade Brasileira de Cardiologia (DEIC/SBC) - Presidência,⁵ Rio de Janeiro, RJ – Brazil

The purpose of the Brazilian Society of Cardiology (SBC) is to expand and disseminate knowledge on Cardiovascular Science and to make each cardiologist aware of the activities intended to promote cardiovascular health in Brazilian society. Since its foundation, SBC has been stimulating research and dissemination, among civil society, of epidemiological and preventive matters related to the treatment of cardiovascular diseases, including heart failure (HF). HF has been identified as a cardiovascular epidemic throughout the world and involves important aspects on morbidity, mortality and healthcare costs, being little recognized among individuals, members of our society, healthcare managers and policy makers. The increasing prevalence of HF is due to population aging and the growth of risk factors, such as obesity, systemic arterial hypertension and diabetes mellitus, as well as increased survival of patients with heart diseases, such as congenital heart disease and ischemic heart disease. Worldwide, about 26 million adults have HF and forecasts indicate that the prevalence tends to increase by 25% by 2030.¹

Within the scenario, it should be underscored that HF with preserved ejection fraction (HFPEF) needs greater recognition and prevention strategies by general practitioners, geriatricians and cardiologists.² The syndrome presents asymptomatic stages and a symptomatic form, and preventive and therapeutic measures are able to reduce the progression of the disease and morbimortality. Outbreaks of acute HF and decompensation promote recurrence in emergency rooms and hospital admissions that promote worsening of the condition, where the outcome can be abrupt due to pump failure or sudden death.³ In this decade, initiatives in different countries, led by cardiology associations and societies, have promoted activities to warn the population and health professionals regarding early detection, complementary tests and access to medications and treatment based on scientific evidence.

Under the leadership of the Department of Heart Failure of the Brazilian Society of Cardiology (DEIC/SBC), Brazil is engaged in promoting activities related to this topic, by creating the awareness day, to be celebrated each year on July 9th, the

data of birth of genius and pioneer cardiovascular translational scientist Carlos Justiniano Ribeiro das Chagas. This year, two dates are very remarkable: 140 years of the birth of professor and researcher Carlos Chagas and 110 years of the discovery of Chagas' disease. A unique fact in the history of Medicine, in which a single researcher describes the vector, the etiological agent, identifies the hosts and attempts to identify the clinical forms of the disease.⁴ The theme of Chagas' disease, in our country, remains contemporary, not only in the search for new treatments,⁵ vaccines and new forms of contamination, such as the oral route described in the north, northeast and south regions, involving sugarcane and açai, reported this year in the Brazilian Archives of Cardiology,⁶ but also in the current outbreak of acute Chagas' disease in Pernambuco, still in the process of clarification. Tribute has been paid to scientist Carlos Chagas in Brazil in several ways (Figure 1), but we have identified that his contribution to cardiology and HF was definitive and important, representing his remarkable name for this noble cause in our country.

With continental dimensions, our country has a great diversity of lifestyle, environmental, socioeconomic and cultural risk factors, as well as the composition of its health system (access, organization of the healthcare network, financing, availability of technological resources and professionals). IC clinics that can offer multiprofessional care have been shown to reduce admissions and improve quality of life. Cardiac rehabilitation has proven effectiveness, but it is not yet available, causing the low inclusion of people in these programs. Different factors may explain the variability of the number of hospital admissions, early retirement for HF and use of resources – heart transplantation, surgery, cardiac catheterization, pacemaker implantation, defibrillators and healthcare costs. According to Araujo et al.,⁷ the direct cost of treatment is represented mainly by hospitalization and costs with medication. However, indirect costs represent economic impacts similar to direct costs. A recent study estimates that about BRL 22.1 billion/US\$ 6.8 billion were spent on the treatment of HF in our country in 2015 alone,⁸ and could represent 68% of hospitalization costs, as seen in the USA and Europe, due to costly diagnostic techniques, high cost of medications, interventions and devices. Therefore, reducing hospital admissions is critical for reducing costs, in addition to the physical and psychological limitations that can be worsened in these patients, particularly depressive symptoms and anxiety. The increasing prevalence of hospital admissions, estimated in some centers at up to 25%, and high hospital morbidity and mortality rates, especially in the presence of comorbidities, such as renal failure, have been documented in different studies.^{9,10} Private sector data are beginning to be described and published as those present at the Observatory of the National Association

Keywords

Heart Failure/epidemiology; Heart Failure /prevention and control; Risk Factors; Chagas Cardiomyopathy/physiopathology; Chagas Disease/epidemiology.

Mailing Address: Evandro Tinoco Mesquita •

Ministro Otávio Kely, 500 1506, Icarái, Niterói, RJ – Brazil

E-mail: etmesquita@gmail.com

DOI: 10.5935/abc.20190137

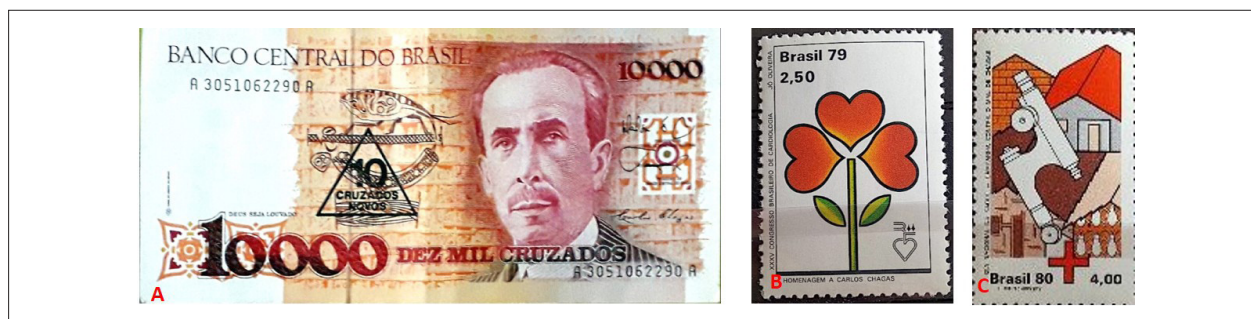


Figure 1 – A) The ten thousand Brazilian cruzeiros note in honor of Carlos Chagas – “The notable physician in his laboratory” – launched in 1988. B) Stamp commemorating the 35th Brazilian Conference on Cardiology in honor of Carlos Chagas, 1979. C) Commemorative Stamp of the National Health Day – Chagas’ Disease, 1980.

of Private Hospitals (ANAHP) on patients admitted due to HF in a group of hospitals with accreditation and protocols to serve this population. Data from the 2019 Observatory reveal,¹¹ in 2017 and 2018, respectively, a median of stay of 7.56 and 6.72 (SD = 3.72), inpatient mortality of 7.49% and 5.26%, rate of use of angiotensin converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARA) on discharge of 89.43% and 88.41% (SD = 17.40%) and rate of use of betablockers at discharge of eligible patients of 93.29% and 94.29% (SD = 10.09%).

Being aware of this variability in healthcare and outcomes of HF is important for us to help improve the quality of care in our country. Through the BREATHE registry, DEIC has studied patients from different regions of the country and verified the high in-hospital mortality among those admitted with acute HF associated with low rate of prescription of evidence-based medicines in Brazil.¹² Fonseca et al.¹³ have found that through the demographic changes observed over the years in continental Portugal and the clinical practices currently employed, in about 40 years, the country will have half a million patients undergoing treatment for HF, highlighting the extreme need for raising people’s awareness, improving reference levels and healthcare so that the burden of the syndrome in the country may have its representativity diminished. They also stress the importance of optimizing healthcare strategies, organizing essential healthcare services, promoting adjustments while respecting regional characteristics, by avoiding a single model of work, reiterating the need for organized discussions at all levels of healthcare to the population.¹⁴ Corroborating this need for adjusting and regionalizing healthcare, Kaufman et al.¹⁵ argue that, considering the last 12 years of HF in Brazil, the Southeast region presented the highest number of hospital admissions, accounting for 41.4% of hospital admissions according to DATASUS data. In the characterization of this population in South America, Brazil contributes with most of the studies, accounting for 64% of the production of published data, being the only one to present its incidence in a population study.¹⁶

DEIC/SBC has continuously used its Acute and Chronic Heart Failure Guideline published in 2018 to ensure the best scientific evidence available on diagnosis and treatment.³ Regarding the role of diagnosis and beginning of treatment, many patients are still diagnosed during their first admission for acute HF. This demonstrates the need for greater investment in the continuing education of general practitioners, clinicians

and cardiologists working at family clinics, basic health units and practices, and in the multidisciplinary and organized healthcare, in order to coordinate the line of care, palliative care protocols, in short, medical care based on HF teams. In the experience of Germany, 63.2% of the new cases were identified in a doctor’s office and 94% of diagnosed patients received their first prescription from the general practitioner. Cases of HF in hospitalized patients, where previous diagnosis was given by a non-specialist in 70.7%, reaffirm the strategy of investing in mechanisms of recognition of the disease in this group of professionals.¹⁷ In our country, we do not have a healthcare process based on the full care of patients in a standardized way, which leads to delayed diagnosis in many patients, without the recognition of signs and symptoms by individuals and caregivers. This said, the process of education, recognition of the main symptoms and treatment are imperative needs, and initiatives that can promote knowledge about HF are fundamental for improving the quality of care. Besides those, access to complementary tests that demonstrate the objective presence of HF, such as the biomarkers brain natriuretic peptide (BNP) and N-terminal prohormone of brain natriuretic peptide (NT pro-BNP), and imaging scans for the correct handling of these patients.

It is necessary to emphasize the importance of obtaining population registries to draw up a global picture of HF. China, Malaysia and South Africa, involved in the International Congestive Heart Failure (Inter-CHF) study, show that although socioeconomic similarities are distinct in etiology, comorbidities, sociodemographic characteristics and outcomes,¹⁸ some comorbidities, such as diabetes mellitus, atrial fibrillation and chronic kidney disease, have been shown to be independent factors associated with hospital admissions and mortality in some samples. Hospital admissions and visits to the emergency room were also shown to be associated with outcomes in several studies.¹⁹ Despite these well-established comorbidities correlated to outcomes, we found a group whose role is not yet properly characterized, such as sleep apnea, iron deficiency, sarcopenia and chronic obstructive pulmonary disease. Further studies regarding the contribution of these comorbidities in mortality still need to be developed.²⁰ Learning about disparate socioeconomic conditions that modify the incidence of HF in different regions in the same country can also be derived from population registries. Even in health systems such as that of the UK, it can be

seen that social inequalities interfere with accessibility and lead to a consequent increase in cases of the syndrome.²¹ As for mortality, using hospital records and death certificates for the mapping out HF, we have observed that, so it can be better characterized, we need to validate a standardized registration methodology using more accurate statistical analyses. The inconsistencies between hospital records and reports of cause of death are presented as a window of opportunity for the implementation of studies to improve quantification in all regions of Brazil.²² Along with the Brazilian Heart Failure Network (REBRIC), we intend to mobilize all the instances involved in healthcare, disseminating ideas and sharing knowledge to improve healthcare.²³

HF specialists and cardiologists have the important challenge, at the present time, of organizing the health assistance process in the coordination of lines and resources, aiming at expanding the connection with general practitioners, emergency surgeons, geriatricians and hospitalists, promoting the improvement of clinical outcomes and the patient's journey. The project that we call the HF Map will be one of the priorities of the Department of Heart Failure of the Brazilian Society of Cardiology for 2020-2021, following the consolidated model of comprehensive epistemological assessment of HF figures in our country, tested by the European

Society of Cardiology (ESC) and by the European Society of Heart Failure (ESHF/ESC).²⁴ This will be done through a digital platform that will collect data from different regions in order to quantify and make available the figures of this epidemic in our country. This platform will be implemented in 2020 and will include national data from the public and private sectors, from regulated organizations and scientific publications, which will be evaluated by data scientists, cardiovascular epidemiologists and clinical and population health researchers. Within this plan, the 1st Registry of Cardiomyopathies and Myocarditis in Children and Adolescents will be carried out in collaboration with the Group of Studies in Cardiomyopathies (GEMIC/SBC), aiming at mapping out and describing this population to contribute with better proposals of continuing medical education, clinical diagnostic criteria and creation of specialized centers of treatment and care.

In short, the construction of a day of awareness on HF (Figure 2), on Carlos Chagas' date of birth, aims at raising the awareness for healthcare professionals, patients, relatives and society in general; and the decision makers in health, who can make decisions and take actions that can influence the evolution of this important cardiovascular epidemic in Brazil. This is one of DEIC's commitments, which is in lined with the mission of SBC, and supported by the National Academy of Medicine.



Figure 2 – This is the logo of the heart failure awareness day campaign promoted by DEIC/SBC, supported by the National Academy of Medicine.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail*. 2016;18(8):891-975.
2. Jorge AJ, Rosa ML, Fernandes CM, Freire MC, Rodrigues RC, Correia DM, et al. Estudo da Prevalência de Insuficiência Cardíaca em Indivíduos Cadastrados no Programa Médico de Família - Niterói. Estudo Digitalis: desenho e método. *Rev Bras Cardiol*. 2011;24(5):320-5.
3. Montera MW, Bocchi EA, Clausell NO, Albuquerque DC, Rassi S, et al. Diretriz Brasileira de Insuficiência Cardíaca Crônica e Aguda. *Arq Bras Cardiol*. 2018;111(3):436-539.
4. Bestetti RB, Restini CB, Couto LB. Descobertas de Carlos Chagas como Pano de Fundo para a Construção Científica da Cardiopatia Chagásica Crônica. *Arq Bras Cardiol*. 2016;107(1):63-70.
5. Morillo CA, Marin-Neto JA, Avezum A, Sosa-Estani S, Rassi A, Rosas F, et al. Randomized Trial of Benznidazole for Chronic Chagas' Cardiomyopathy. *N Engl J Med*. 2015;373(14):1295-306.
6. Ortiz JV, Pereira BV, Couceiro KD, Silva MR, Doria SS, Silva PR, et al. Cardiac Evaluation in the Acute Phase of Chagas' Disease with Post-Treatment Evolution in Patients Attended in the State of Amazonas, Brazil. *Arq Bras Cardiol*. 2019;112(3):240-6.
7. Araujo DV, Tavares LR, Veríssimo R, Ferraz MB, Mesquita ET. Cost of heart failure in the Unified Health System. *Arq Bras Cardiol*. 2005;84(5):422-7.
8. Stevens B, Pezzullo L, Verdian L, Tomlinson J, George A, Bacal F. The Economic Burden of Heart Conditions in Brazil. *Arq Bras Cardiol*. 2018;111(1):29-36.
9. Reis AP, Souza AG, Ferreira GC, Oliveira JM, Venancio JC, Fernandes TM, et al. Prevalence of heart failure in Brazil: a problem of public health. *Rev Educ Saúde*. 2016;4(2):24-30.
10. Wajner A, Zuchinali P, Olsen V, Polanczyk CA, Rohde LE. Causes and Predictors of In-Hospital Mortality in Patients Admitted with or for Heart Failure at a Tertiary Hospital in Brazil. *Arq Bras Cardiol*. 2017;109(4):321-30.
11. (ANAHP) Associação Nacional de Hospitais Privados. Observatório 2018. [Cited in 2019 Jun 21]. [Available from: https://rdstation-static.s3.amazonaws.com/cms%2Ffiles%2F62776%2F1559915480OBS2019-WEB-v4_compressed.pdf]
12. Albuquerque DC, Neto JD, Bacal F, Rohde LE, Bernardes-Pereira S, Berwanger O, et al. I Brazilian Registry of Heart Failure - Clinical Aspects, Care Quality and Hospitalization Outcomes. *Arq Bras Cardiol*. 2015;104(6):433-42.
13. Fonseca C, Brás D, Araújo I, Ceia F. Insuficiência cardíaca em números: estimativas para o século XXI em Portugal. *Rev Port Cardiol*. 2018;37(2):97-104.
14. Brito D, Cernadas R, Ferreira J, Franco F, Rodrigues T, et al. Pela melhoria do tratamento da insuficiência cardíaca em Portugal – documento de consenso. *Rev Port Cardiol*. 2017;36(1):1-8.
15. Kaufman R, Azevedo VM, Xavier RM, Gueller M, Chaves RB, Castier MB. Insuficiência cardíaca: análise de 12 anos da evolução em internações hospitalares e mortalidade. *Int J Cardiovasc Sci*. 2015;28(4):276-81.
16. Ciapponi A, Alcaraz A, Calderón M, Matta MG, Chaparro M, Soto N, et al. Carga de enfermedad de la insuficiencia cardiaca en America Latina: revision sistematica y metanálisis. *Rev Esp Cardiol*. 2016;69(11):1051-60.
17. Störk S, Handrock R, Jacob J, Walker J, Calado F, Lahoz R, et al. Epidemiology of heart failure in Germany: a retrospective database study. *Clin Res Cardiol*. 2017;106(11):913-22.
18. Dokainish H, Teo K, Zhu J, Roy A, Al-Habib K, ElSayed A, et al. Heart failure in low- and middle-income countries: Background, rationale, and design of the International Congestive Heart Failure Study (INTER-CHF). *Am Heart J*. 2015;170(4):627-34.e1.
19. Farré N, Vela E, Clèries M, Bustins M, Cainzos-Achirica M, Enjuanes C, et al. Real-world heart failure epidemiology and outcome: A population-based analysis of 88,195 patients. *PLoS One*. 2017;12(2):e0172745.
20. Von Haehling S. Co-morbidities in heart failure beginning to sprout—and no end in sight? *Eur J Heart Fail*. 2017;19(12):1566-8.
21. Conrad N, Judge A, Tran J, Mohseni H, Hedgecott D, Crespillo AP, et al. Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. *Lancet*. 2018;391(10120):572-80.
22. Bierrenbach AL, Pereira AG, Cátia M, Marinho MF, Moreira PG, Barboza FE. Redistribuição de óbitos por insuficiência cardíaca usando dois métodos: *linkage* de registros hospitalares com dados de atestados de óbito e de causas múltiplas de morte. *Cad Saúde Pública*. 2019; 35(5):e00135617.
23. (REBRIC). Rede Brasileira de Insuficiência Cardíaca. [Cited in 2019 Jun 21]. [Available from: <https://rebric.com.br/>]
24. Timmis A, Townsend N, Gale C, Grobbee R, Maniadakis N, Flather M, et al. European Society of Cardiology: Cardiovascular Disease Statistics 2017. *Eur Heart J*. 2018;39(7):508-79.



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

Non-Pharmacological Treatment of Cardiovascular Disease | Importance of Physical Exercise

Mariana Janini Gomes, Luana Urbano Pagan, Marina Politi Okoshi^{ID}

Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP), Botucatu, SP – Brazil

Cardiovascular diseases are currently the major health problem and are directly involved in more than 17 million deaths each year, which represents 50% of all deaths from noncommunicable diseases.¹ In addition to their effects on individual well-being, cardiovascular diseases are responsible for a high economic impact. A recently published study showed that in Brazil, only four diseases – arterial hypertension, myocardial infarction, atrial fibrillation and heart failure – reached an estimated total financial cost of 56.2 billion reais in the year 2015.¹

The treatment of cardiovascular diseases involves the use of specific drugs and adherence to non-pharmacological interventions.² This Editorial will be dedicated to the role of physical exercise in the treatment of cardiovascular diseases.

Brazil has a prominent position worldwide regarding the study of the effects of physical exercise in different clinical conditions. The practice of physical exercises has been recommended for decades for health promotion and treatment of several cardiovascular diseases. The regular practice of exercises results in several benefits, such as increased functional capacity and improved body composition, insulin resistance, endothelial function, arterial hypertension, antioxidant status, and quality of life.³⁻⁹

Concerning heart failure, exercises have been recommended for almost three decades in the treatment of stable patients. In addition to increasing effort tolerance, it improves the quality of life and reduces hospitalizations for heart failure.² Despite a large number of studies evaluating the effects of exercise, its influence on different situations of cardiac aggression has yet to be fully clarified.¹⁰

In articles recently published in this journal, the role of exercise and its molecular mechanisms of action have been evaluated in different heart disease experimental models.^{3,5,11-13} The beneficial effects on cardiac remodeling have been frequently observed, such as attenuation of myocardial hypertrophy and left ventricular dysfunction.^{7,14} However, unexpected results have drawn attention to the need for better clarification of the subject. For instance, Rodrigues et al.¹³ submitted beta-adrenergic receptor knockout mice, which

may develop heart failure, to treadmill training for eight weeks. Surprisingly, the trained knockout animals showed a higher increase in functional capacity and myocardial contractility than the trained control animals. As an exaggerated contractility stimulus may lead to deterioration of cardiac function in the long-term, additional studies are required to define the role of exercise in cardiac function in beta-adrenergic receptor knockout mice in later life.

Topics of great uncertainty regarding exercise prescription include the intensity and duration of exercise. Recently, Ellingsen et al.¹⁵ published the first multicenter randomized trial comparing the effects of high-intensity interval training (HIIT) with those of continuous training at moderate intensity or recommendation for regular exercises in patients with heart failure with reduced ejection fraction. In both specific training groups, the results were only moderately better than the recommendation for regular exercise. Moreover, 51% of patients in the HIIT group exercised below the prescribed heart rate, and 80% of the individuals from continuous training group at moderate intensity trained at a frequency above their target. Thus, considering that HIIT was not superior to the continuous training group at moderate intensity in reducing the remodeling process or improving clinical outcomes, and the difficulty in attaining adherence to the prescribed intensity, the authors recommend that continuous training at moderate intensity should remain as the standard modality for patients with chronic heart failure.

Another factor that remains to be clarified is whether the practice of exercise in short and intense periods repeated throughout the day, called accumulated exercise, can be an alternative for sedentary individuals. Martinez et al.¹⁶ observed that both continuous and accumulated exercise improved the physical fitness of healthy rats. However, only the continuous exercise was able to reduce body weight gain and improve endothelial function. Aortas obtained from the group submitted to continuous exercise showed a reduction in the contractile response to norepinephrine and an increase in acetylcholine-induced relaxation, which was not observed in the group trained using accumulated exercise.¹⁶

A greater consensus is observed in the literature regarding the role of physical exercise on the vascular system. Lemos et al.¹² showed that regular aerobic exercise for nine weeks led to the attenuation of sympathetic activity and reduction in vascular resistance, thus contributing to a decrease in blood pressure in spontaneously hypertensive rats. Resistance training was also effective in improving the bradycardic response and baroreflex sensitivity of spontaneously hypertensive rats.¹¹ However, the fact that these effects were not accompanied by a reduction in systemic blood pressure¹¹ suggests that aerobic exercise is superior to resistance training for arterial hypertension control.

Keywords

Cardiovascular Diseases; Heart Failure; Exercise/prevention and control; Physical Fitness; Ventricular Remodeling; Quality of Life.

Mailing Address: Marina Politi Okoshi •

Departamento de Clínica Médica. Rubião Júnior, S/N. Postal Code 18618-000, Rubião Júnior, Botucatu, SP – Brazil
E-mail: mpoliti@fmb.unesp.br

DOI: 10.5935/abc.20190118

Despite the great advances regarding the understanding of physical exercise effects on the healthy cardiovascular system or that submitted to different types of aggression, we are still far from clarifying the physical exercise mechanisms of action and from scientifically defining the best prescription for patients with cardiovascular disease.

Acknowledgements

We would like to thank Fundação de Amparo à Pesquisa do Estado de São Paulo – FAPESP (Proc. N. 2014/21972-3 and 2014/23592-3); Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPq (Proc. N. 310876/2018-4 and 153424/2018-4).

References

1. Stevens B, Pezzullo L, Verdian L, Tomlison J, George A, Bacal F. et al. The economic burden of heart conditions in Brazil. *Arq Bras Cardiol.* 2018;111(1):29-36.
2. Comitê Coordenador de Cardiologia; Rohde LEP, Montera MW, Bocchi EA, Colanfranceschi AS, Freitas A, Fraz AS, et al. Diretriz brasileira de insuficiência cardíaca crônica e aguda. *Arq Bras Cardiol.* 2018;111(3):436-539.
3. Winter SCN, Macedo RM, Francisco JC, Santos PC, Lopes APS, Meira LF, et al. Impact of a high-intensity training on ventricular function in rats after acute myocardial infarction. *Arq Bras Cardiol.* 2018;110(4):373-80.
4. Ghorbanzadeh V, Mohammadi M, Dariushnejad H, Abhari A, Chodanai L, Mohaddes G. Cardioprotective effect of crocin combined with voluntary exercise in rat: Role of Mir-126 and Mir-210 in heart angiogenesis. *Arq Bras Cardiol.* 2017; 109(1):54-62.
5. Naderi R, Mohaddes G, Mohammadi M, Alihemmati A, Khamaneh A, Ghyasi R, et al. The effect of garlic and voluntary exercise on cardiac angiogenesis in diabetes: The role of Mir-126 and Mir-210. *Arq Bras Cardiol.* 2019;112(2):154-62.
6. Gomes MJ, Martinez PF, Campos DHS, Pagan LV, Bonomo C Lima AR, et al. Beneficial effects of physical exercise on functional capacity and skeletal muscle oxidative stress in rats with aortic stenosis-induced heart failure. *Oxid Med Cell Longev.* 2016;2016:8695716.
7. Pagan LU, Damatto RL, Cezar MD, Lima AR, Bonomo C, Campos DH, et al. Long-term low intensity physical exercise attenuates heart failure development in aging spontaneously hypertensive rats. *Cell Physiol Biochem.* 2015;36(1):61-74.
8. Gomes MJ, Martinez PF, Pagan LU, Damatto RL, Cezar MDM, Lima Ar, et al. Skeletal muscle aging: Influence of oxidative stress and physical exercise. *Oncotarget.* 2017;8(12):1235-45.
9. Reyes DRA, Gomes MJ, Rosa CM, Pagan LU, Zanati SG, Damatto RL, et al. Exercise during transition from compensated left ventricular hypertrophy to heart failure in aortic stenosis rats. *J Cell Mol Med.* 2019;23(2):1235-45.
10. Cattadori G, Segurini C, Picozzi A, Padeletti L, Anzà C. Exercise and heart failure: An update. *ESC Heart Fail.* 2018;5(2):222-32.
11. Gomes MFP, Borges ME, Rossi VA, et al. The effect of physical resistance training on baroreflex sensitivity of hypertensive rats. *Arq Bras Cardiol.* 2017; 108(6):539-45.
12. Lemos MP, Mota GRD, Marocolo M, Moura EOC, Medeiros A. Exercise training attenuates sympathetic activity and improves morphometry of splenic arterioles in spontaneously hypertensive rats. *Arq Bras Cardiol.* 2018;110(3):263-9.
13. Rodrigues AC, Natali AJ, Cunha DN, Costa AJ, Moura AG, Araujo Carneiro JR, M, et al. Moderate continuous aerobic exercise training improves cardiomyocyte contractility in $\beta 1$ adrenergic receptor knockout mice. *Arq Bras Cardiol.* 2018; 110(3):256-62.
14. Cai M, Wang Q, Liu Z, Jia D, Feng R, Tian Z. Effects of different types of exercise on skeletal muscle atrophy, antioxidant capacity and growth factors expression following myocardial infarction. *Life Sci.* 2018 Nov 15;213:40-9.
15. Ellingsen O, Halle M, Conraads V, Stevien A, Dalin N, Delagardelle C, et al. SMARTEX Heart Failure Study (Study of Myocardial Recovery After Exercise Training in Heart Failure) Group. High-intensity interval training in patients with heart failure with reduced ejection fraction. *Circulation.* 2017; 135(9):839-49.
16. Martinez JE, Taipeiro EF, Chies AB. Effects of continuous and accumulated exercise on endothelial function in rat aorta. *Arq Bras Cardiol.* 2017;108(4):315-22.



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

Characterization of Decellularized Human Pericardium for Tissue Engineering and Regenerative Medicine Applications

Luciana Wollmann, Paula Suss,¹⁰ João Mendonça, Cesar Luzia, Andressa Schittini, George Willian Xavier da Rosa,¹⁰ Francisco Costa, Felipe F. Tuon

Pontifícia Universidade Católica do Paraná, Curitiba, PR – Brazil

Abstract

Background: Pericardium tissue allograft can be used for surgical repair in several procedures. One of the tissue engineering strategies is the process of decellularization. This process decreases immunogenic response, but it may modify the natural extracellular matrix composition and behavior.

Objective: The aim of this study was to evaluate the effectiveness of cell removal, maintenance of extracellular matrix properties and mechanical integrity of decellularized human pericardium using a low concentration solution of sodium dodecyl sulfate.

Methods: Decellularization was performed with sodium dodecyl sulfate and ethylenediaminetetraacetic acid. Histological analysis, DNA quantification, evaluation of glycosaminoglycans and collagen were performed. Biomechanical assay was performed using tensile test to compare the decellularization effects on tissue properties of tensile strength, elongation and elastic modulus. $P < 0.05$ was considered significant.

Results: There was reduction in visible nuclei present in pericardium tissue after decellularization, but it retained collagen and elastin bundles similar to fresh pericardium. The DNA contents of the decellularized pericardium were significantly reduced to less than 511.23 ± 120.4 ng per mg of dry weight ($p < 0.001$). The biomechanical assay showed no significant difference for fresh or decellularized tissue.

Conclusion: The decellularization process reduces cell content as well as extracellular matrix components without changing its biomechanical properties. (Arq Bras Cardiol. 2019; 113(1):11-17)

Keywords: Pericardium; Tissue Banks; Tissue Engineering/trends; Cell Separation; Glycosaminoglycans.

Introduction

Development of extracellular matrix-derived bioscaffolds has been highly desired for applications in tissue engineering and regenerative medicine.¹ These scaffolds can be obtained from a variety of allogeneic or xenogeneic tissue sources and from several different species.² However, biomaterial antigenicity represents the primary barrier to expanding the use of xenogeneic tissues in clinical practice.³

Pericardium is a collagen-rich biological tissue containing glycoproteins and glycosaminoglycans³ and is readily available, easy to handle, and pliable. Human pericardium can be used as a patch for heart surgeries⁴ and non-heart surgeries (Peyronie's disease,⁴ glaucoma and corneal surgery,^{5,6} to cover exposed scleral buckles⁷ and oculoplastic surgery.⁸

Human pericardium patch is a well-recognized material for cardiovascular repair.⁴ The physicochemical features

of autologous pericardium used for repair include fresh pericardium^{9,10} and glutaraldehyde-treated pericardium.¹¹ However, the use of fresh autologous untreated pericardium can result in tissue retraction, thickening, fibrosis and loss of pliability¹² and the use of glutaraldehyde-treated autologous pericardium can result in calcification.¹³

The main obstacle is the development of biocompatible and functional extracellular matrix-derived bioscaffold. The use of biological tissues increases the potential risks of pathogen transmission¹⁴ and inflammatory or immunogenic response.^{2,15} Decellularization techniques have been used to minimize these issues.¹⁶

Tissue decellularization can be performed by using different protocols, detergent extraction or enzymatic extraction with hypotonic or hypertonic washings and physical (agitation, sonication, mechanical pressure or freeze-thawing) treatments.² The ideal decellularization method must remove all antigenic components (nucleic acids, cell membranes, cytoplasmic structures, lipids and soluble matrix) from the tissue without damaging extracellular matrix structure and integrity.^{17,18} However, the decellularization process can modify the natural extracellular matrix composition, as well as mechanical and structural characteristics.¹⁹ Furthermore, high levels of donor variability to naive ECM composition undoubtedly lead to different ECM fractional composition post-decellularization. Hence, ECM standardization as

Mailing Address: Felipe F. Tuon •

Imaculada Conceição, 1155. Postal Code 80215-901, Curitiba, PR – Brazil

E-mail: flptuon@gmail.com

Manuscript received June 22, 2018, revised manuscript August 13, 2018, accepted September 19, 2018

DOI: 10.5935/abc.20190094

a biomaterial remains elusive.¹⁸ Several procedures of decellularization has been described, but this study evaluated low concentration of detergent.

The aim of this study was to evaluate the effectiveness of cell removal, maintenance of extracellular matrix properties and mechanical integrity of decellularized human pericardium using a low concentration solution of sodium dodecyl sulfate.

Methods

All procedures followed the Brazilian National Regulations and Guidelines according to Regulatory Ordinance nº 2.600, published on October 21, 2009 and ANVISA Resolution - RDC nº 55, published on December 11, 2015. This study was approved by the Ethical Committee of Pontifícia Universidade Católica do Paraná (approval number 1.455.773).

Donors

Pericardium from 14 non heart-beating and heart-beating donors were obtained by convenience sampling under aseptic conditions. After heart explantation, the organ was placed in a tub with saline solution at 2-8 °C and the intracavitary blood clots washed. The organ was placed in a sterilized plastic bag, immersed in ice-cold isotonic solution in sufficient quantity to maintain the organ totally immersed. This packaging was sealed, then packaged in two more plastic bags (configuring triple packaging), as each bag must be properly tied or sealed. The triple package containing the organ was placed in an airtight container and placed inside the thermal box in the middle of ice and transported to the human tissue bank (HTB). Dissection was carried out within 48 h after cardiac arrest. Tissue underwent dissection to remove connective tissue and the pericardial sac was cut into strips individually stored in saline solution at 2-8 °C. Blood samples were tested for HIV, HTLV I/II, HBV, HCV, syphilis, cytomegalovirus (IgM and IgG), toxoplasmosis (IgM and IgG) and Chagas' disease. Donors data were retrieved from their medical records. Positive serology was criteria for rejection except toxoplasma IgG and cytomegalovirus IgG.

Microbiological control

Before tissue preparation, 30 mL of transport solution (sterile NaCl 0.9% solution) were obtained aseptically in a Class II-A laminar airflow cabinet with a syringe and distributed equally over to a recipient with 90 mL of thioglycolate (Laborclin, Pinhais, Brazil), 90 mL of tryptic soy broth (Laborclin, Pinhais, Brazil) and 90 mL of Sabouraud (Laborclin, Pinhais, Brazil) for bacteriological and mycological testing. The samples were cultured for 14 days at 35°C, 22°C and 22°C, respectively. Cultures were examined daily for visual evidence of turbidity. The ones that showed microorganisms growth were identified for genus and species level.

Tissue preparation and decontamination

Adherent adipose tissue was dissected with the aid of scissors and forceps. The pericardium was divided into two portions to characterize fresh pericardium versus decellularized

pericardium. The pericardia were decontaminated in a RPMI 1640 (Sigma-Aldrich, St. Louis, USA) medium with antibiotics (240 µg/mL cefoxitin, 50 µg/mL vancomycin, 120 µg/mL lincomycin and 100 µg/mL polymyxin B) and were kept between 24 and 48 hours at 2-8°C. Persistent positive cultures after decontamination were used as exclusion criteria.

Decellularization

Briefly, the pericardia were treated under shaking conditions with a solution of 0.1% sodium dodecyl sulfate (SDS) (w/v) (Sigma-Aldrich, St. Louis, USA) and 7 mM ethylenediaminetetraacetic acid (Sigma-Aldrich, St. Louis, USA) for 24 hours at room temperature. Then, they were washed with 70% ethanol (v/v) for 24 hours at room temperature followed by 10 days of washing with sodium chloride (NaCl) 0.9% solution (Baxter International, Deerfield, USA) to remove residual substances and cellular debris.

Histological analysis

Longitudinal 3.0 mm cuts with were fixed with neutral buffered formaline 10%, subsequently embedded in paraffin and 4-µm thick sections were taken. Pericardial morphological integrity was analyzed with hematoxylin and eosin (H&E) and Russell-Movat pentachrome (RMP) dyes using an optical microscope BX51 (Olympus Tokyo, Japan). Fresh pericardium was used as control to evaluate changes caused by decellularization. Slides were scanned using an Axio Scan.Z1 slide scanner (Carl Zeiss Microscopy GmbH, Jena, Germany) and subsequent image preparation was performed using software Zen lite (Carl Zeiss, Jena, Germany).

DNA extraction and quantification

DNA quantification was used to determine the total remaining DNA by comparing the levels in fresh and decellularized pericardium. Tissue samples were weighted, purified and rehydrated using a QIAGEN DNeasy Blood and Tissue Kit (QIAGEN, Valencia, USA) according to the recommended protocol. The concentration of extracted DNA was determined using a Nanodrop spectrophotometer (ThermoFisher Scientific, Wilmington, USA). Extracted DNA sample (1 µL) was loaded onto the Nanodrop and the absorbance was determined at 260 nm. Four readings were taken for each sample and the mean was considered as the absorbance of the sample. DNA concentration was calculated and expressed as micrograms per milligram of dry tissue.

Biochemical Characterization

Sulfated Glycosaminoglycans (sGAG)

The pericardium was digested with papain solution at 60°C for 6 h. Papain (Sigma, St. Louis, MO) was dissolved at 400 mg/mL in 0.1 M phosphate buffer (pH 6.0) with 5 mM cysteine hydrochloride and 5 mM EDTA. The lysates were used for detection of the sGAG amount. The amount of sGAG was measured using a Blyscan sGAG assay kit (Biocolor, Newtownabbey, UK) according to the manufacturer's manual. The tissue lysate was mixed with Blyscan dye to

bind the GAG. The GAG-dye complex was then collected by centrifugation. Subsequently, the supernatant was removed and the tube drained, and the dissociation reagent was added. Then solution was transferred into a 96-well plate. Absorbance against the background control was obtained at a wavelength of 656 nm on a Versamax spectrophotometer (Molecular Devices, Sunnyvale, USA). The sGAG amount was calculated based on a standard curve obtained with the standard sGAG supplied with the kit.

Collagen

Collagen contents in the pericardium were determined using the Sircol collagen assay (Biocolor, Newtownabbey, UK) according to the manufacturer's instructions. The pericardium were incubated for 48 h at 48°C in 0.5 M acetic acid containing 0.1 mg/ml pepsin. The samples were added to Sircol dye reagent, and collagen-dye complexes formed and precipitated out from the soluble unbound dye. After centrifugation, the pellet was washed once with Acid-Salt Wash Reagent and suspended in alkali reagent. The solution was transferred to a 96-well plate and the absorbance was read at 550 nm on a Versamax spectrophotometer (Molecular Devices, Sunnyvale, USA). The amount of collagen was calculated based on a standard curve obtained with standard bovine type I collagen supplied with the kit.

Cytotoxicity Assay

Cytotoxicity of decellularized pericardium was performed in accordance with ISO 10993/5. L929 fibroblasts (ATCC cell line CCL 1, NCTC clone 929) were seeded in 6-well plates (Nest) at a density of 1×10^5 cells/well. Each well, with inner diameter of 35 mm, received 4 mL of DMEM + 2mM Glutamine + 10% Fetal Bovine Serum. The plates were incubated for 48 h at 37°C in an atmosphere of $5\% \pm 0.5\% \text{ CO}_2$ in the air, until a monolayer, with greater than 80% confluence. The medium was removed from the wells and replaced with agar 1.8% added to neutral red dye 0.01%. Samples in triplicate, positive, negative and blank controls on the agar overlay featured 6-well plates. After an incubation period of 24 h at 37 °C in a humidified atmosphere of $5\% \pm 0.5\% \text{ CO}_2$ in air, the inhibition zone around the samples was measured, as neutral red is free from dead cells. The biological reactivity of the samples was scored from 0 to 4 in accordance with the following criteria: 0 = absent cytotoxicity (absence of a zone of lysis underneath the sample); 1 = slight (zones of cell lysis underneath the sample only); 2 = mild (zones of cell lysis ≤ 5 mm from the sample); 3 = moderate (zones of cell lysis > 5 mm and ≤ 10 mm from the sample); 4 = severe (zones of cell lysis > 10 mm, but not involving the entire well). In addition, the wells were examined with an inverted microscope (Nikon Eclipse TS 100; Nikon) to observe cell changes.

Biomechanical Assay

The biomechanical assay of human pericardium was performed with tensile test to compare the decellularization effects on tissue properties of tensile strength, elongation and elastic modulus. An EMIC DL 500 universal testing machine

was used to perform the tests. The sample quantity of fresh and decellularized tissue used was 8 and 6 respectively, and collagen fibers traction direction was random. The dumbbell-shaped sample was based on the ASTM D1708-13 standard because of the small-size tissue available to the tests. To obtain the samples, it was necessary to manufacture a steel rule die according to standard specifications, which was used to cut the pericardium. Before each test, sample thickness, width and initial length values were provided to the equipment. Thickness and width are necessary to calculate the cross-sectional area and consequently the stress (equation 1). Initial length is necessary to calculate the strain and consequently the elongation percentage (equation 2). Thickness was measured with a thickness gauge at three points of the tissue. Pre-load of 0.1 N and 5 mm/min velocity were applied to the test.

Equation 1. Stress calculation.

$$\sigma = F/A$$

where:

σ is the stress in megapascal [MPa];

F is the force in newton [N] and

A is the cross-sectional area in square millimeter [mm²].

Equation 2. Calculation of elongation percentage.

$$\%EI = (\Delta L/L_i) \times 100 = \epsilon \times 100$$

where:

%EI is the elongation percentage;

ΔL is the variation of sample length in millimeters [mm];

L_i is the initial sample length in millimeters [mm] and

ϵ is the strain in millimeters per millimeter [mm/mm].

Statistical analyses

Continuous variables with normal distribution were expressed as mean $\pm$ SD and median and interquartile range for non-normal distribution, while categorical variables were expressed as frequencies or percentages. Mann-Whitney was used for non-normal distribution of continuous variables, t-test for normal distribution of continuous variables. All tests were two-tailed, and p value < 0.05 was considered significant. Statistical analyses were carried out using SPSS 23.0.

Results

Donors' characteristics

The mean age was 39 ± 14 years ranging between 17 and 59 years old. Regarding race, among the samples used, there was a preponderance of donors declared white, 86% ($n = 12$) of the total and 7% ($n = 1$) declared themselves as Afro-descendants. An additional 7% ($n = 1$) was not recorded in the forms.

Microbiological assessment

Transport solution was positive in 5 samples from 14. *Corynebacterium* spp., *Streptococcus salivarius*, *Staphylococcus*

aureus, *Klebsiella oxytoca*, *Anaerococcus prevotii* and *Leuconostoc pseudomesenteroides* were the bacteria identified. Other microbiological tests after decontamination and decellularization were negative.

Analysis of extracellular matrix integrity and cell removal

H&E and DAPI staining revealed a reduction in visible nuclei present in pericardium tissue after decellularization (Figure 1A, B, D and E). The main extracellular matrix components were examined in RMP staining (collagen - yellow, elastin - black, and glycosaminoglycans – blue). The structure of the decellularized pericardium extracellular fibers retained collagen and elastin bundles similar to fresh pericardium. However, there was increased thickness of the decellularized tissue compared with the fresh one (Figure 1 C and F).

DNA quantification

Fresh pericardium tissue with complete cellular contents had a DNA amount as high as 1591 ± 726 ng per mg dry weight. The DNA contents of the decellularized pericardium were significantly reduced to less than 511.23 ± 120.4 ng per mg dry weight. ($p < 0.001$) (table 1).

Effect of decellularization on sulfated glycosaminoglycan and collagen content

The concentration of collagen per mg of dry weight of human pericardium tissue before and after decellularization was 126.9 ± 45.8 and 138.3 ± 58.6 $\mu\text{g}/\text{mg}$ of dry tissue, respectively ($p = 0.716$). Quantification of collagen content in fresh pericardium demonstrated a small increase in the collagen content of the tissue after decellularization. sGAG content was determined to be 0.64 ± 0.50 and 0.02 ± 0.06 sGAG per mg of dry tissue, respectively. ($p = 0.014$)

Cytotoxicity assay

Decellularized human pericardium ($n = 3$) was incubated for 24 h (Figure 2A). The samples from the decellularized pericardium had no effect on the cells, as indicated by their normal cell morphology after incubation for 24 h. The negative control also had no effect on the cells (Figure 2B). In contrast, latex (positive control) caused cell death (Figure 2C).

Biomechanical Assay

Average human pericardium thickness showed no significant difference (Welch's t test: $p = 0.9518$), which was 0.45 ± 0.06 mm for fresh tissue and 0.44 ± 0.05 mm for the decellularized tissue. Tensile strength, elongation and elastic modulus are presented as column scatter plot graphs (Figure 3A, B and C) showing the mean and standard deviation. The mean difference among the groups was not significant for all properties ($p > 0.05$). The average stress-strain curve of fresh and decellularized tissue are presented in Figure 3D, which shows the typical behavior for biological tissues as previously described.²⁰ It is also possible to observe that the behavior of curves was similar in the initial phase until transition phase, keeping approximate parallels until maximum stress.

Discussion

The aim of decellularization is to minimize the immune response by completely removing cellular components as well as preserving the physical characteristics of the extracellular matrix.^{2,21} The ideal decellularized tissue must achieve complete decellularization and preservation of the extracellular matrix for biomechanical stability and function, but it is recognized that any decellularization protocol may result in extracellular matrix disruption and potential loss of surface structure and composition.²

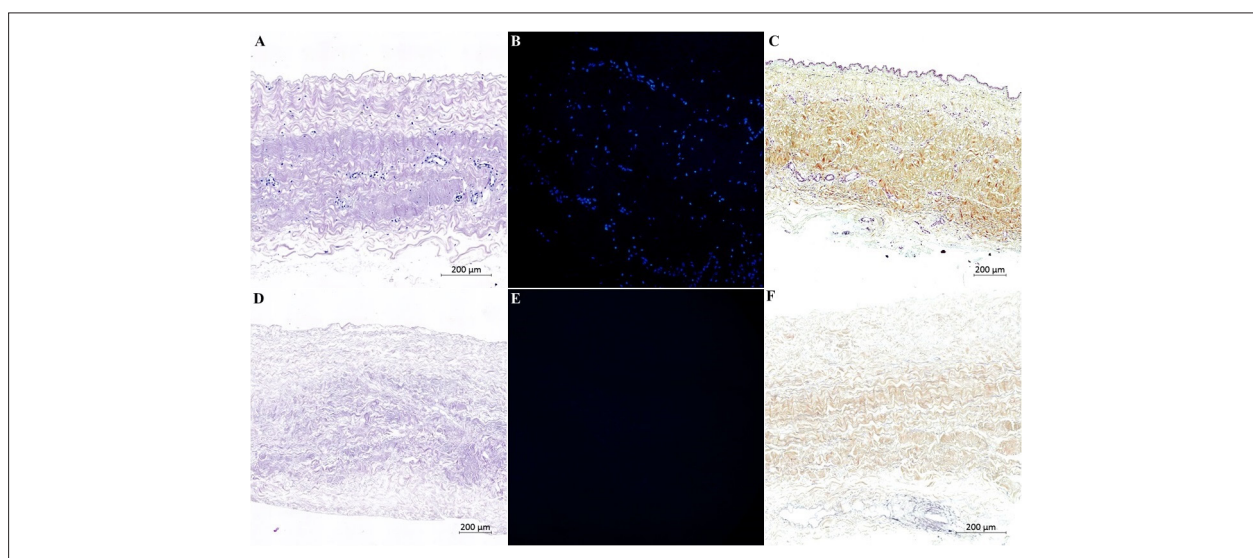


Figure 1 – Histological characterization of fresh and decellularized human pericardium. H&E and DAPI staining showed no evidence of cell in the tissue sections (D and E). H&E and RMP staining showed that decellularization did not affect the structure of collagen bundles. However there was a reduction of collagen and increased thickness of the decellularized tissue compared with the fresh one (D and F).

Table 1 – Collagen, glycosaminoglycan and DNA content of fresh and decellularized human pericardium

	Collagen $\mu\text{g}/\text{mg}$	Glycosaminoglycan $\mu\text{g}/\text{mg}$	DNA ng/mg
Fresh pericardium	126.9 ± 45.8	0.64 ± 0.50	1591 ± 726.0
Decellularized pericardium	138.3 ± 58.6	0.02 ± 0.06	511.23 ± 120.4
P value	0.716	0.014	< 0.001

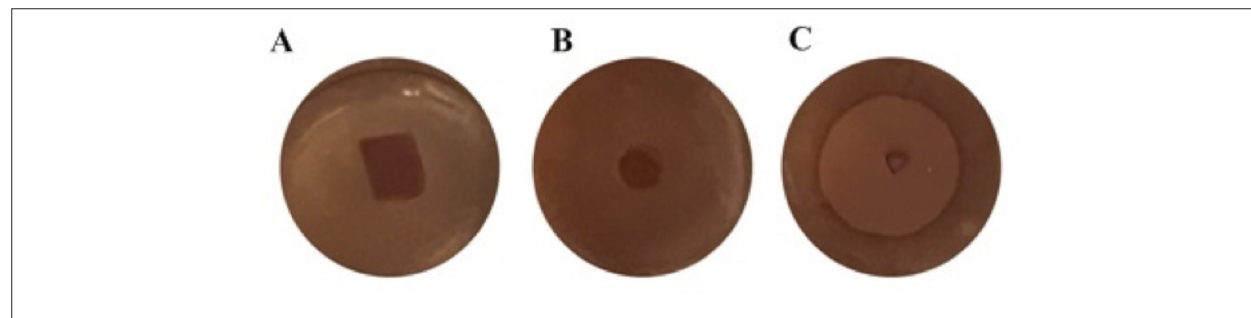


Figure 2 – Agar overlay cytotoxicity assay. Testing image after 24 hours in contact with agar-overlay. Decellularized human pericardium (A), negative control (B) and positive control (C).

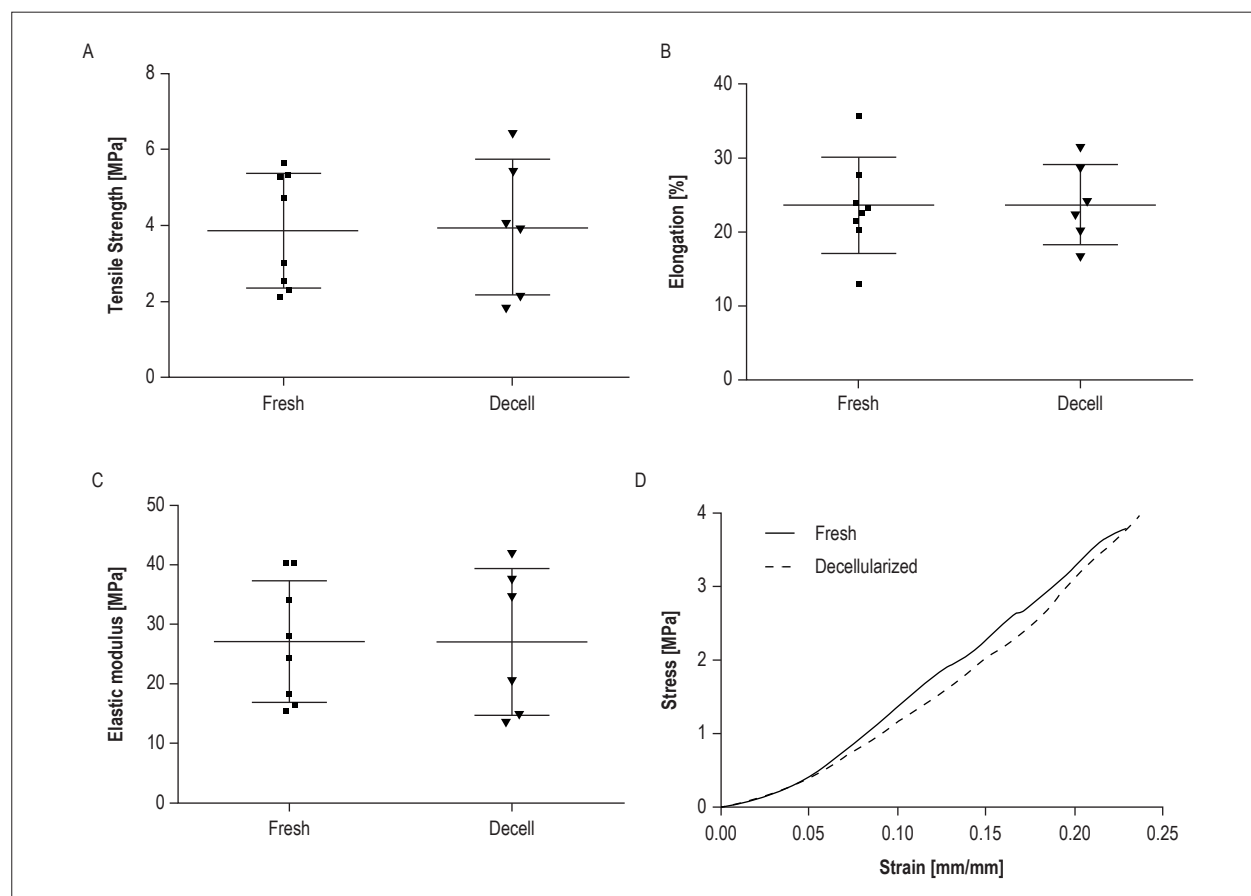


Figure 3 – Graphical representation of the mechanical parameters obtained for fresh and decellularized human pericardium. (A) Tensile strength [MPa]; (B) elongation [%]; (C) elastic Modulus [MPa] and (D) the curves indicate the mean stress-strain behavior of fresh and decellularized human pericardium

In the histological analysis, this study revealed that most cellular components were removed, but some components of the extracellular matrix were reduced and the decellularized tissue thickness increased. Similar findings were reported by Courtman et al.²² with a 3-fold increase in tissue thickness. However, Mirsadraee et al.²³ did not observe any significant changes using an SDS-based decellularization protocol in the histological analysis comparing both fresh and decellularized human pericardium.

In this study, decellularized human pericardium got a small increase in the collagen content and a significant reduction in sGAG content. In agreement with our observation, Mendoza-Novelo et al.²⁴ reported a reduction in fresh pericardium tissue sGAG content after decellularization with surfactant tridecyl alcohol ethoxylate and reversible alkaline swelling.²⁴ On the other hand, a study by Mirsadraee et al.²³ reported a small increase in hydroxyproline and GAG content in the tissue after decellularization.²³ The authors concluded that increase of hydroxyproline was due to a relative increase in the ratio of these molecules regarding total dry weight, due to the loss of soluble proteins and cell components.

In order to ensure adequate residual removal, contact cytotoxicity assays were performed to determine the effect of any chemical residuals in the decellularized tissue on the growth of cultured L929 cells. Assay results showed that cells grew well in contact with samples of decellularized human pericardium, indicating that the decellularized tissues were non-toxic. This result also correlates with previous study on decellularized human pericardium.²³

We compared the mechanical properties of fresh and decellularized pericardium and there were no significant differences between them. SDS-based decellularization by itself does not modify the performance of human pericardium as for the parameters of tensile strength, elongation and elastic modulus. These results were previously assessed in the acellular human pericardium.²³ In a more recent work, the biomechanical properties of decellularized and cryopreserved human pericardium were preserved in comparison with fresh tissue.²⁵

Nevertheless, this study did not evaluate the outcome of implanted human decellularized pericardium. In vitro

analysis is not enough to confirm complete decellularization. The maintenance of extracellular matrix in this study does not allow to determine that all molecular and physiological properties are really ideal.

Conclusion

The decellularization process reduces cell content as well as extracellular matrix components and increases thickness without changing the biomechanical properties of the decellularized tissue compared with the fresh one. Decellularized human pericardium may be a suitable candidate for the production of extracellular matrix-derived scaffolds for tissue engineering and regenerative medicine applications.

Author contributions

Conception and design of the research: Wollmann L, Suss P; Acquisition of data: Wollmann L, Suss P, Mendonça J, Luzia C, Schittini A, Rosa GWX; Analysis and interpretation of the data: Luzia C, Tuon FF; Statistical analysis and Critical revision of the manuscript for intellectual content: Tuon FF; Obtaining financing: Costa F; Writing of the manuscript: Suss P, Tuon FF.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by Fundo Nacional de Saúde - Ministério da Saúde – projeto nº 814611/2014.

Study Association

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

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Lu H, Hoshiba T, Kawazoe N, Chen G. Autologous extracellular matrix scaffolds for tissue engineering. *Biomaterials*. 2011;32(10):2489-99.
2. Crapo PM, Gilbert TW, Badylak SF. An overview of tissue and whole organ decellularization processes. *Biomaterials*. 2011;32(12):3233-43.
3. Platt J, DiSesa V, Gail D, Massicot-Fisher J, National Heart L, Blood Institute H, et al. Recommendations of the National Heart, Lung, and Blood Institute Heart and Lung Xenotransplantation Working Group. *Circulation*. 2002;106(9):1043-7.
4. Hellstrom WJ, Reddy S. Application of pericardial graft in the surgical management of Peyronie's disease. *J Urol*. 2000;163(5):1445-7.
5. Yoo C, Kang SY, Eom YS, Kim HM. Temporary Repair of Corneal Perforation Tutoplast((R))-Processed Pericardium Graft. *Ophthalmic Surg Lasers Imaging*. 2010 Mar;1-3.
6. Yoo C, Kwon SW, Kim YY. Pericardium plug in the repair of the corneoscleral fistula after Ahmed Glaucoma Valve explantation. *Korean J Ophthalmol*. 2008;22(4):268-71.
7. Weissgold DJ, Millay RH, Bochow TA. Rescue of exposed scleral buckles with cadaveric pericardial patch grafts. *Ophthalmology*. 2001;108(4):753-8.
8. Seider N, Beiran I, Kaltreider SA. One medial triangular Tutoplast sling as a frontalis suspension for adult myogenic blepharoptosis. *Acta Ophthalmol Scand*. 2006;84(1):121-3.
9. Evans CF, DeFilippi CR, Shang E, Griffith BP, Gammie JS. Fresh autologous pericardium for leaflet perforation repair in mitral valve infective endocarditis. *J Heart Valve Dis*. 2013;22(4):560-6.

10. Takahashi H, Kadowaki T, Maruo A, Okita Y, Oshima Y. Mitral commissural repair with autologous fresh pericardium in an infant. *Ann Thorac Surg.* 2014;97(3):1064-6.
11. Thudt M, Papadopoulos N, Monsefi N, Miskovic A, Karimian-Tabrizi A, Zierer A, et al. Long-Term Results Following Pericardial Patch Augmentation for Incompetent Bicuspid Aortic Valves: A Single Center Experience. *Ann Thorac Surg.* 2017;103(4):1186-92.
12. Shomura Y, Okada Y, Nasu M, Koyama T, Yuzaki M, Murashita T, et al. Late results of mitral valve repair with glutaraldehyde-treated autologous pericardium. *Ann Thorac Surg.* 2013;95(6):2000-5.
13. Fukunaga N, Matsuo T, Saji Y, Imai Y, Koyama T. Mitral Valve Stenosis Progression Due to Severe Calcification on Glutaraldehyde-Treated Autologous Pericardium: Word of Caution for an Attractive Repair Technique. *Ann Thorac Surg.* 2015;99(6):2203-5.
14. Greenwald MA, Kuehnert MJ, Fishman JA. Infectious disease transmission during organ and tissue transplantation. *Emerg Infect Dis.* 2012;18(8):e1.
15. Badylak SF, Gilbert TW. Immune response to biologic scaffold materials. *Semin Immunol.* 2008;20(2):109-16.
16. Dohmen PM. Clinical results of implanted tissue engineered heart valves. *HSR Proc Intensive Care Cardiovasc Anesth.* 2012;4(4):225-31.
17. Rippel RA, Ghanbari H, Seifalian AM. Tissue-engineered heart valve: future of cardiac surgery. *World J Surg.* 2012;36(7):1581-91.
18. Aamodt JM, Grainger DW. Extracellular matrix-based biomaterial scaffolds and the host response. *Biomaterials.* 2016 Apr;86:68-82.
19. Gilbert TW, Sellaro TL, Badylak SF. Decellularization of tissues and organs. *Biomaterials.* 2006;27(19):3675-83.
20. Hasan A, Ragaert K, Swieszkowski W, Selimovic S, Paul A, Camci-Unal G, et al. Biomechanical properties of native and tissue engineered heart valve constructs. *J Biomech.* 2014;47(9):1949-63.
21. Min BJ, Kim YJ, Choi JW, Choi SY, Kim SH, Lim HC. Histologic Characteristics and Mechanical Properties of Bovine Pericardium Treated with Decellularization and alpha-Galactosidase: A Comparative Study. *Korean J Thorac Cardiovasc Surg.* 2012;45(6):368-79.
22. Courtman DW, Pereira CA, Kashaf V, McComb D, Lee JM, Wilson GJ. Development of a pericardial acellular matrix biomaterial: biochemical and mechanical effects of cell extraction. *J Biomed Mater Res.* 1994;28(6):655-66.
23. Mirsadraee S, Wilcox HE, Korossis SA, Kearney JN, Watterson KG, Fisher J, et al. Development and characterization of an acellular human pericardial matrix for tissue engineering. *Tissue Eng.* 2006;12(4):763-73.
24. Mendoza-Novelo B, Avila EE, Cauch-Rodriguez JV, Jorge-Herrero E, Rojo FJ, Guinea GV, et al. Decellularization of pericardial tissue and its impact on tensile viscoelasticity and glycosaminoglycan content. *Acta Biomater.* 2011;7(3):1241-8.
25. Vinci MC, Tessitore G, Castiglioni L, Prandi F, Soncini M, Santoro R, et al. Mechanical compliance and immunological compatibility of fixative-free decellularized/cryopreserved human pericardium. *PLoS One.* 2013;8(5):e64769.



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

Decellularization of Human Pericardium with Potential Application in Regenerative Medicine

Estela de Oliveira Lima,¹^{ORCID} Adriana Camargo Ferrasi,¹ Andreas Kaasi²^{ORCID}

Universidade Estadual Paulista Júlio de Mesquita Filho - FMB - Depto. Clínica Médica,¹ Botucatu, SP – Brazil

Santa Casa de Misericórdia de São Paulo - Instituto de Pesquisa, Inovação Tecnológica e Educação,² São Paulo, SP – Brazil

Short Editorial related to the article: Characterization of Decellularized Human Pericardium for Tissue Engineering and Regenerative Medicine Applications

Regenerative medicine is an interdisciplinary branch of the biomedical sciences that is showing, through the transposition of basic research into the clinic, great potential for therapeutic application, and the field is consequently becoming an important frontman for Translational Medicine. The essence of regenerative medicine consists of the repair or replacement of tissues and organs in which there is structural and functional deficiency. With a view of achieving this objective, several approaches have been proposed, including therapies that include genes, cells, biologic and synthetic *scaffolds*, which may or may not take part of a tissue engineering strategy.¹ When dealing with synthetic scaffolds, it is possible to manipulate and control structural and mechanical properties, nonetheless, it is not possible to guarantee the same functional capacity as natural tissue.² In addition, one of the great challenges is minimizing the risk of immunogenic reactions triggered by the repair scaffold's composition.³ Owing to the challenges associated with the reestablishment on a functional and structural level of the cell microenvironment, the interest in scaffolds based on natural extracellular matrix (ECM) has increased considerably.

With a view of obtaining a biomaterial closely approximating tissues or organs having suffered damage, be it structural or functional, yet at the same time presenting safety from an immunological point of view, a new technology for clinical applications of ECM has been proposed – the decellularization of tissues and organs from human or animal donors. This technology makes use of physical, chemical and/or biochemical methods to eliminate cells from the target tissue/organ, be it xenogeneic or allogeneic, whose antigens represent an elevated risk of immunogenic reaction. The process seeks to ensure immunologic safety and the preservation of basic structural and functional components of the ECM, such as proteins, collagen and glycosaminoglycans (GAGs). The end product is a three-dimensional ECM scaffold with analogous shape to the original tissue, with preserved ultrastructural architecture and with greater biocompatibility and potential of tissue regeneration when compared to synthetic scaffolds.⁴

Keywords

Regenerative Medicine; Pericardium; Tissue Scaffolds; Cells; Heart Valves/surgery; Translational Medical Research; Biocompatible Materials.

Mailing Address: Estela de Oliveira Lima •

Universidade Estadual Paulista Júlio de Mesquita Filho - FMB - Departamento de Clínica Médica - Distrito de Rubião Júnior, s/n. Postal Code 18618-687, Botucatu, SP – Brazil
E-mail: estela.lima@unesp.br

DOI: 10.5935/abc.20190130

Pericardial tissue, mainly of bovine origin, has been widely used in cardiac surgery, whether for substitution of cardiac valves or for the repair of congenital disorders. Its fibroserous structure, rich in elastic fibres and collagen bundles, bestows upon the pericardium an elevated resistance to mechanical stress, and this resistance, together with the capability of uniform suture retention, represent essential characteristics for application in cardiovascular surgeries.^{5,6}

With a view of reducing the probability of immunogenic response and rejection of the graft, the pericardium may be submitted to different treatments, among others the tissue fixation using glutaraldehyde, which is routinely used. While this method leads to lower immunogenicity of the tissue, the cytotoxicity and propensity of calcifications are two important inconveniences associated with this technique.^{7,8} Faced with these problems, other methods are being developed to improve on the safe utilization of pericardium in cardiac surgery, including decellularization. One of the most established techniques for this purpose is the treatment of the tissue using ionic detergents, such as sodium dodecyl sulfate (SDS). Whereas this decellularization agent is capable of removing undesirable natural components, such as antigenic molecules, it may also lead to structural alterations in the pericardial ECM; the loss of GAGs and important signaling proteins being notable examples. The structural damage caused by the treatment with SDS may impair the ideal *in situ* or *in vitro* recellularization of the scaffold, as well as altering the mechanical properties of the matrix, such as elasticity and extensibility.⁹

The original work presented by Wollmann et al.¹⁰ in this issue promotes the approach of human pericardium decellularization using a reduced quantity of detergent for application as a cardiovascular patch. The work presents itself with a view of minimizing the impact of the technique and to obtain a human ECM of better quality, non-toxic and that may retain as much as possible the original architecture and composition. The proposed methods exhibit a considerable removal of cell components, including DNA, the presence of which was reduced to approximately one-third of the original content. The tissue was also assessed with respect to cytotoxicity, and it was shown that no cytotoxic effects were seen *in vitro*. This observation brings a great stimulus for the even deeper investigation of the technique, such as the undertaking of *in vivo* tests with a view of future clinical application. Moreover, the treatment employed did not alter the composition of the pericardium with respect to the components elastin (qualitative assessment) and collagen (quantitative and qualitative assessment). The treatment did present a significant quantitative reduction in GAGs, which is well known from the literature when the decellularization

is performed using SDS detergent (revised by Scarritt et al.¹¹). Despite the structural changes with respect to GAGs, the biomechanical behavior of the matrix was similar to that of fresh tissue, and this enables use in the treatment of tissues that suffer intense mechanical loads, such as those encountered in the cardiovascular system.

We observe that one of the field's great challenges is to unmask the best method of obtaining intact scaffolds. For that purpose, the concentration of the reagents can be modulated to guarantee the ideal ECM composition, and when it is optimized on the basis of the philosophy of "less is more", the reagents fail considerably in removing completely cell debris, containing cellular DNA. Conversely, when the concentrations used are higher, the opposite is true.¹² Considering that the success of the techniques of decellularization is directly associated to minimal change in composition, structure and mechanics of tissues, the work of Wollmann et al.¹⁰ is in line with the requirements of perfecting the methods of obtaining decellularized pericardium.

In the article, Wollmann et al.¹⁰ investigate mainly the effect of a concentration of SDS described as "low", of 0.1% (w/v). That concentration is unquestionably low compared to the concentration of 1% used in, for example, decellularization of porcine kidneys.¹³ Other authors have adopted the descriptor "low concentration" for 0.5%, also for porcine kidneys.¹⁴ The concept of "low concentration" should be understood in the context of the tissue to be decellularized. For example, 0.1% may be a low concentration for a sub-millimetric tissue,

such as pericardium, whereas 0.5% may equally be low for a centrimetric organ, such as the kidney. In addition to the challenge of customizing the concentration to the tissue to be decellularized, the variability between donors hampers the standardization of a scalable decellularization process and suggests that the path to clinical translation requires a customized and not necessarily standardized approach.

The use of patches in cardiac surgery is already a well-established practice, however, the most widely used biological material is of xenogeneic origin and is not submitted to the process of decellularization, increasing the risk of surgical reinterventions.^{3,15} The prospect of employing a decellularized pericardial patch, whose structural components are satisfactorily preserved and the antigenic molecules properly eliminated, is consequently of great interest for clinical application. These characteristics have the potential to enhance the signaling in the tissue for the recruitment and adhesion of cells from the recipient patient's own tissue, to maintain ideal mechanical characteristics, in addition to reducing the immunogenicity of the graft.¹⁶ All this would elevate the durability of the graft, favor adequate tissue regeneration and reduce the propensity to fibrosis and calcification, improving the quality of life of the patient. Considering that cardiovascular disease is the driver of the main causes of death worldwide (31%),¹⁷ developing strategies that lead to products biocompatible for this application and more similar to natural tissue is of great importance to regenerative medicine and, as a consequence, new alternatives are emerging in the quest for an ideal cardiac biomaterial.

References

- Hacker MC, Krieghoff J, Mikos AG, Synthetic Polymers. In *Principles of Regenerative Medicine*, 3 ed. Atala A, Ed. Academic Press: 2018; p. 1428.
- Hench LL, Polak JM. Third-Generation Biomedical Materials. *Science*. 2002;295(5557):1014-7.
- Griffiths LG, Choe LH, Reardon KF, Dow SW, Christopher Orton E. Immunoproteomic identification of bovine pericardium xenoantigens. *Biomaterials*. 2008;29(26):3514-20.
- Gilbert TW, Sellaro TL, Badylak SF. Decellularization of tissues and organs. *Biomaterials*. 2006;27(19):3675-83.
- Vinci MC, Tessitore G, Castiglioni L, Prandi F, Soncini M, Santoro R, et al. Mechanical compliance and immunological compatibility of fixative-free decellularized/cryopreserved human pericardium. *PLoS One*. 2013;8(5):e64769.
- Inoue H, Iguro Y, Matsumoto H, Ueno M, Higashi A, Sakata R. Right hemi-reconstruction of the left atrium using two equine pericardial patches for recurrent malignant fibrous histiocytoma: Report of a case. *Surg Today*. 2009;39(8):710-2.
- Ma B, Wang X, Wu C, Chang J. Crosslinking strategies for preparation of extracellular matrix-derived cardiovascular scaffolds. *Regen Biomater*. 2014;1(1):81-9.
- Schoen FJ, Levy RJ. Calcification of tissue heart valve substitutes: progress toward understanding and prevention. *Ann Thorac Surg*. 2005;79(3): 1072-80.
- Gilpin A, Yang Y. Decellularization Strategies for Regenerative Medicine: From Processing Techniques to Applications. *Biomed Res Int*. 2017 Apr;2017:9831534.
- Wollmann L, Suss P, Mendonça J, Luzia C, Schittini A, Rosa GW. Caracterização do Pericárdio Humano Descelularizado para Engenharia de Tecidos e Aplicações de Medicina Regenerativa. *Arq Bras Cardiol*. 2019; 113(1):11-17.
- Scarritt ME, Pashos NC, Bunnell BA. A Review of Cellularization Strategies for Tissue Engineering of Whole Organs. *Front Bioeng Biotechnol*. 2015 Mar;3:43.
- Akhyari P, Aubin H, Gwanmesia P, Barth M, Hoffmann S, Huelsmann J, et al. The quest for an optimized protocol for whole-heart decellularization: a comparison of three popular and a novel decellularization technique and their diverse effects on crucial extracellular matrix qualities. *Tissue Eng Part C Methods*. 2011;17(9):915-26.
- de Souza FR, Dalboni MA, Kaasi A, Pestana JO, Vieyra, AR, de Souza NK. *Rapid Protocol of Porcine Kidney Decellularization*. *Journal of Biomimetics, Biomaterials and Biomedical Engineering*. 2018 Aug;38:67-74.
- Poornejad N, Momtahan N, Salehi AS, Scott DR, Fronk CA, Roeder BL, et al. Efficient decellularization of whole porcine kidneys improves reseeded cell behavior. *Biomed Mater*. 2016;11(2):025003.
- Ashcraft TM, Jones K, Border WL, Eghtesady P, Pearl JM, Khoury PR, et al. Factors affecting long-term risk of aortic arch reoperation after the Norwood procedure. *Ann Thorac Surg*. 2008;85(4):1397-401; discussion 1401-2.
- Hussein KH, Park KM, Kang KS, Woo HM. Biocompatibility evaluation of tissue-engineered decellularized scaffolds for biomedical application. *Mater Sci Eng C Mater Biol Appl*. 2016 Oct;67:766-778.
- World Health Organization. (WHO). World Heart Day. Scale up prevention of heart attack and stroke, 2017 [cited in 2017 Sep 29]. Available from: https://www.who.int/cardiovascular_diseases/world-heart-day/en/



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

Application of Risks Scores in Acute Coronary Syndromes. How Does ProACS Hold Up Against Other Risks Scores?

Júlio Gil,¹ Luísa Abreu,¹ Hugo Antunes,¹ Maria Luísa Gonçalves,¹ Maria Inês Pires,¹ Luís Ferreira dos Santos,¹ Carla Henriques,^{2,3} Ana Matos,² José Costa Cabral,¹ Jorge Oliveira Santos¹

Hospital de São Teotónio,¹ Viseu – Portugal

Instituto Politécnico de Viseu e CI&DETS,² Viseu – Portugal

Centro de Matemática da Universidade de Coimbra (CMUC),³ Coimbra – Portugal

Abstract

Background: Multiple risk scores (RS) are approved in the prediction of worse prognosis in acute coronary syndromes (ACS). Recently, the Portuguese Journal of Cardiology has proposed the ProACS RS.

Objective: Application of several validated RS, as well as ProACS in patients, admitted for ACS. Evaluation of each RS's performance in predicting in-hospital mortality and the occurrence of all-cause mortality or non-fatal ACS at one-year follow-up and compare them to the ProACS RS.

Methods: A retrospective study of ACS was performed. The following RS were applied: GRACE, ACTION Registry-GWTG, PURSUIT, TIMI, EMMACE, SRI, CHA₂DS₂-VASC-HS, C-ACS and ProACS. ROC Curves were created to determine the predictive power for each RS and then were directly compared to ProACS.

Results: The ProACS, ACTION Registry-GWTG and GRACE showed a c-statistics of 0.908, 0.904 and 0.890 for predicting in-hospital mortality, respectively, performing better in ST-segment elevation myocardial infarction patients. The other RS performed satisfactorily, with c-statistics over 0.750, apart from the CHA₂DS₂-VASC-HS and C-ACS which underperformed. All RS underperformed in predicting worse long-term prognosis revealing c-statistics under 0.700.

Conclusion: ProACS is an easily obtained risk score for early stratification of in-hospital mortality. When evaluating all RS, the ProACS, ACTION Registry-GWTG and GRACE RS showed the best performance, demonstrating high capability of predicting a worse prognosis. ProACS was able to demonstrate statistically significant superiority when compared to almost all RS. Thus, the ProACS has showed that it is able to combine simplicity in the calculation of the score with good performance in predicting a worse prognosis. (Arq Bras Cardiol. 2019; 113(1):20-30)

Keywords: Acute Coronary Syndrome/prognosis; ST Elevation Myocardial Infarction; Hospital Mortality, Risk Assessment/methods; Survival Rate/methods.

Introduction

Cardiovascular disease is the most common cause of death worldwide.^{1,2} In the past three to four decades, studies have shown a significant reduction in acute and long-term mortality by acute coronary syndromes (ACS).¹⁻³ This is attributed to improvements in medical therapy and invasive strategies.¹⁻³ However, ACS represent a heterogeneous group, with varying risk of morbimortality.¹⁻⁴ Several risk stratification models have been developed to determine which patients carry a higher probability of worst outcome.³⁻¹³ Early risk stratification is crucial to ensure a tailored approach to each individual patient, weighing both the risks and benefits of each treatment option.^{1,2}

Recently, there has been a systematic approach to risk assessment, with the creation of a myriad of risks scores (RS).³⁻¹³ Perhaps, the Global Registry of Acute Coronary Events (GRACE) Risk Score⁶ is the most widely recognized RS in ACS. According to the most recent European guidelines, the GRACE risk score is recommended when stratifying risk in ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction, and/or unstable angina (NSTEMI/UA).^{1,2} However, there are several other known RS, such as: the Thrombolysis in Myocardial Infarction (TIMI) for STEMI;⁷ the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy (PURSUIT);⁵ the Simple Risk Index (SRI);⁸ the Evaluation of the Methods and Management of Acute Coronary Events (EMMACE);⁹ and more recently, the Canada Acute Coronary Syndrome (C-ACS),¹⁰ the CHA₂DS₂-VASC-HS score,¹¹ and the ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry-GWTG.¹²

In 2016, the Portuguese Journal of Cardiology published a new risk score, formulated using the Portuguese Registry on Acute Coronary Syndromes. The Portuguese Registry of Acute Coronary Syndromes was established in 2002,¹⁴

Mailing Address: Júlio Gil •

Hospital de São Teotónio - Av. Rei D. Duarte. 3504 509 – Viseu – Portugal

Email: juliogilpereira@gmail.com

Manuscript received July 26/07/2018, revised manuscript October 02, 2018, accepted October 10, 2018

DOI: 10.5935/abc.20190109

under the auspice of the Portuguese Society of Cardiology. It is an observational, multicentric, nationwide prospective study in which each hospital participates with data from all patients admitted for ACS. The group developed the simple but effective ProACS risk score for predicting in-hospital mortality, which can be easily applied even in a pre-hospital setting.³

The objective of this article is to calculate all of the RS in patients admitted for ACS, in a single-centre study. The authors evaluate each RS's performance in predicting in-hospital mortality and compare them specifically to the ProACS RS. The authors also determine each RS's performance at predicting worse outcome in STEMI and NSTEMI/UA independently. Finally, the authors assess each RS's ability to predict mortality and recurring ACS at one-year follow-up.

Methods

This is a retrospective study of patients admitted for ACS to a Coronary Care Unit of a centralized hospital, from December 2006 to May 2016. Only patients presenting with a history of chest pain at rest or other symptoms suggestive of an ACS with or without new significant ST-segment or T-wave changes, new left bundle branch block or elevated biomarkers of myocardial damage were included. Of the 1714 patients included in the study period, 1452 were selected, with the remaining patients being excluded due to missing data. The population sample of this study was not included in the development cohort used to formulate the ProACS risk score,³ although it has been included in the validation cohorts.

The following RS were calculated for all patients: GRACE, TIMI for STEMI, PURSUIT, SRI, EMMACE, C-ACS, CHA₂DS₂-VASc-HS, ACTION Registry-GWTG and ProACS. All RS were calculated using data from the initial clinical history, electrocardiogram and laboratory values collected on admission. All patients included were followed up for at least one year or until the occurrence of a major event. The primary endpoint of this study was in-hospital mortality and the combination of all-cause mortality or non-fatal ACS at one-year follow-up.

Statistical analysis

Categorical variables were characterized by percentages. Group comparisons, with respect to these variables, were performed through chi-square or Fisher's exact test. Numeric continuous variables were expressed as mean $\pm$ standard deviation and RS as median with interquartile range, given their ordinal nature. Group comparisons were achieved through the Mann-Whitney test since the normality assumption was not satisfied for any of the studied numeric variables. Comparative analyses were carried out in relation to demographic variables, therapeutic strategies and general outcome parameters. The RS was evaluated by receiver operating characteristic (ROC) curves, and their area under the curve (AUC), with respect to their ability to differentiate patients with and without adverse clinical events, regarding in-hospital mortality and the combination of all-cause mortality or non-fatal ACS at one-year follow-up. The comparison of AUCs, for each RS with ProACS, was done by the method

described by DeLong et al.¹⁵ The Hosmer–Lemeshow Test¹⁶ was used to evaluate the goodness of fit for each risk score. Two-sided *p*-values are reported and a *p*-value < 0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 17.0 (SPSS Inc., Chicago, IL, USA) and MedCalc version 18.2.1 (MedCalc Software, Ostend, Belgium).

Results

Baseline characteristics and univariate predictors of worse outcome

A total of 1,452 patients were included in this study. The baseline characteristics are displayed in Table 1. Regarding in-hospital mortality, 6.5% of the patients died. At one-year follow-up, 9.9% of the patients either died or suffered a non-fatal ACS.

Table 2 displays the univariate predictors for in-hospital mortality and for all-cause mortality and non-fatal ACS at one-year follow-up. Regarding in-hospital mortality, it is evident that older patients have higher mortality, with chronic kidney disease being associated with a worse prognosis. The clinical presentation also influences the outcome. Lower blood pressure and higher heart rate, as well as higher Killip–Kimball (KK) class, were linked to a higher mortality rate. It is also evident that lower haemoglobin and higher creatinine, troponin and brain natriuretic peptide values are associated with a worse prognosis, as well as a lower left ventricular ejection fraction. Regarding the occurrence of events at one-year follow-up, older and female patients tend to have higher mortality. NSTEMI/UA is associated with a worse prognosis. Lower diastolic blood pressure, a higher heart rate and KK class are associated with higher rate of events. Concerning past medical history, diabetes mellitus, chronic kidney disease and previous known coronary disease are associated with a worse outcome. A higher rate of events at 1-year follow-up was seen in patients medicated previously to the index event with statin, renin-angiotensin-aldosterone system inhibitors, beta-blocker and antiplatelet therapy. All RS scored significantly higher in the groups with worse outcome, both in in-hospital mortality and at one-year follow-up.

Predictive accuracy of the risk scores

Table 3, Table 4 and Table 5 describe the predictive accuracy and goodness of fit of the RS at predicting in-hospital mortality globally, at predicting in-hospital mortality in the specific group of STEMI and NSTEMI/UA patients individually, and at predicting occurrence of all-cause mortality and non-fatal ACS at one-year follow-up, respectively. The last column of each table shows how the other RS compare to the ProACS score. Figure 1 displays the ROC curves regarding the RS and in-hospital mortality. Figure 2 shows in-hospital mortality in the STEMI and NSTEMI group individually. The long-term prognosis is demonstrated in Figure 3.

The majority of the RS showed a good discriminatory accuracy to predict in-hospital mortality, as demonstrated by c-statistics consistently over 0.700. Notably, three RS outperformed the others, namely the GRACE, ACTION

Table 1 – Characterization of the population (n=1,452)

Male gender, %	70%
Age, years	69.09 ± 13.2
Type of ACS	
STEMI	45.1%
NSTEMI/UA	52.0%
ACS with left bundle branch block	2.3%
ACS with pacing rhythm	0.6%
Systolic Blood Pressure at admission, mmHg	140.54 ± 30.4
Diastolic Blood Pressure at admission, mmHg	81.79 ± 17.7
Heart rate, beats per minute	79.29 ± 21.1
Killip-Kimbal class at admission	
I	70.7%
II	22.0%
III	5.0%
IV	2.3%
Maximum Killip-Kimbal class	
I	57.2%
II	27.3%
III	6.0%
IV	9.4%
Risk Factors	
Hypertension	65.8%
Dyslipidaemia	46.6%
Smoking habits	24.3%
Diabetes mellitus	26.6%
Previous known coronary disease	19.5%
Chronic kidney disease	9.7%
Cerebrovascular disease	9.4%
Previous medication	
Statin	35.0%
iRAAS	48.1%
Beta-blocker	17.5%
Antiplatelet therapy	34.4%
Laboratory values	
Hemoglobin, g/dL	13.95 ± 2.5
Creatinine, mg/dL	1.20 ± 1.6
High sensitivity troponin I at admission, ng/dL	15.92 ± 49.7
Maximum troponin I, ng/dL	69.68 ± 104.7
Brain Natriuretic Peptide, pg/dL	552.58 ± 708.0
Medication and therapeutic strategy during hospitalization	
iRAAS	81.9%
Beta-blocker	59.6%
Nitrates	32.4%
Antiarrhythmics	13.6%

Continuation

Inotropes	12.3%
Invasive strategy	79.9%
Left Ventricular Ejection Fraction, %	53.80 ± 12.3
Hospitalization days	7.3 ± 5.0
Risk Scores	
TIMI for STEMI	5 (3-7)
PURSUIT	13 (10-14)
SRI	26.04 (17.82 – 37.24)
GRACE	144 (112-178.75)
EMMACE	0.15 (0.06 – 0.33)
CHA ₂ DS ₂ -VASC-HS	4 (3-5)
ACTION Registry–GWTG	34 (27-44)
C-ACS	1 (1-1)
ProACS	2 (1-3)
In-hospital Death	6.5%
All-cause mortality and non-fatal ACS at 1-year follow-up	9.9%

ACS: acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction; NSTEMI/UA: non-ST-segment elevation myocardial infarction/unstable angina; iRAAS: renin angiotensin aldosterone system inhibitors. TIMI: Thrombolysis in Myocardial Infarction; PURSUIT: Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy; SRI: Simple Risk Index; GRACE: Global Registry of Acute Coronary Events; EMMACE: Evaluation of the Methods and Management of Acute Coronary Events; C-ACS: Canada Acute Coronary Syndrome. Chronic kidney disease defined as reduction of glomerular filtration rate of under 60 ml/min/1.73 m².

Registry–GWTG and ProACS RS, with c-statistics around 0.900. Most RS, apart from the ProACS (p = 0.031), PURSUIT (p = 0.043), ACTION Registry–GWTG (p = 0.041) and C-ACS (p = 0.003) RS, showed an adequate fit, as demonstrated by a p-value for the Hosmer-Lemeshow (HL) test over 0.05. Comparing ProACS to the other RS revealed a statistically significant superiority of the first to all except the ACTION Registry–GWTG (p = 0.6647) and the GRACE (p = 0.0879).

All RS consistently showed better discriminatory accuracy at predicting in-hospital mortality in STEMI patients. In this population, the ACTION Registry–GWTG and ProACS RS performed incredibly well, with c-statistics of over 0.900. Almost all RS revealed an adequate fit, except for the SRI (p = 0.011), the C-ACS (p = 0.005) and a trend from PURSUIT (p = 0.075). In STEMI patients, the ACTION Registry–GWTG (p = 0.882) and ProACS RS (p = 0.821) showed good fit. The ProACS RS demonstrated statistically significant superior discriminatory accuracy when compared to all other RS, except for ACTION Registry–GWTG (p = 0.2248).

In the NSTEMI population, the RS performed slightly worse when compared to STEMI patients. ProACS, ACTION Registry–GWTG and GRACE scores were the RS with the highest discriminatory accuracy at predicting in-hospital mortality, with c-statistics of 0.898, 0.895 and 0.878 respectively. ProACS also demonstrated significant superiority, except when compared to the aforementioned RS.

Table 2 – Univariate predictors of worse prognosis

	In-Hospital Mortality			1-year Follow-up		
	With events (n = 94)	Without events (n = 1358)	p-value	With events (n = 135)	Without events (n = 1223)	p-value
Male sex, %	70.2%	70.0%	0.97	59.3%	71.2%	0.004
Age, years	76.6 ± 10.2	68.6 ± 13.2	< 0.001	75.4 ± 12.7	67.8 ± 13.1	< 0.001
Type of ACS						
STEMI, %	54.3%	46.9%	0.168	31.1%	48.7%	< 0.001
NSTEMI/UA, %	45.7%	53.1%		68.9%	51.3%	
Systolic Blood Pressure at admission, mmHg	121.6 ± 30	141.9 ± 30	< 0.001	138.7 ± 31.7	142.2 ± 30	0.109
Diastolic Blood Pressure at admission, mmHg	73.2 ± 18.4	82.4 ± 17.5	< 0.001	78.6 ± 17.4	82.9 ± 17.5	0.002
Heart rate, beats per minute	83.9 ± 25.6	79.0 ± 20.7	0.02	85.6 ± 21.1	78.2 ± 20.6	< 0.001
Killip-Kimbal class at admission						
I	34.0%	73.3%	< 0.001	43.0%	76.6%	< 0.001
II	48.9%	20.1%		43.7%	17.5%	
III	7.4%	4.8%		10.4%	4.2%	
IV	9.6%	1.8%		3.0%	1.7%	
> I	66.0%	26.7%	< 0.001	57.0%	23.4%	< 0.001
Maximum Killip-Kimbal class						
I	4.3%	60.9%	< 0.001	29.6%	64.3%	< 0.001
II	12.8%	28.4%		51.9%	25.8%	
III	2.1%	6.3%		13.3%	5.5%	
IV	80.9%	4.5%		5.2%	4.4%	
> I	95.7%	39.1%	< 0.001	70.4%	35.7%	< 0.001
Risk Factors						
Hypertension, %	70.2%	65.5%	0.355	70.4%	65.0%	0.213
Dyslipidemia, %	41.5%	46.9%	0.308	51.9%	46.4%	0.225
Smoking habits, %	16.0%	24.9%	0.051	13.3%	26.2%	0.001
Diabetes Mellitus, %	31.9%	26.2%	0.226	35.6%	25.2%	0.009
Chronic Kidney Disease, %	17.5%	9.1%	0.015	20.4%	7.6%	<0.001
Cerebrovascular disease, %	12.5%	9.2%	0.332	11.5%	8.9%	0.368
Previous known coronary disease, %	19.1%	19.5%	0.931	34.1%	17.9%	< 0.001
More than 3 Risk Factors	34.0%	29.4%	0.339	35.6%	28.7%	0.097
Previous Medication						
Statin, %	36.2%	34.9%	0.803	43.0%	34.0%	0.038
iRAAS, %	55.3%	47.6%	0.015	57.0%	46.6%	0.021
Beta-blocker, %	17.0%	17.5%	0.901	25.2%	16.7%	0.014
Antiplatelet therapy, %	38.3%	34.1%	0.407	58.5%	31.4%	< 0.001
Laboratory values						
Hemoglobin, g/dL	13.3 ± 2.4	14.0 ± 2.5	0.006	12.8 ± 2.1	14.1 ± 2.5	< 0.001
Creatinine, mg/dL	1.56 ± 0.93	1.18 ± 1.6	< 0.001	1.58 ± 1.6	1.13 ± 1.6	< 0.001
Troponin at admission, ng/dL	34.4 ± 72.2	14.6 ± 47.5	< 0.001	23.1 ± 86.1	13.7 ± 41	0.215
Maximum troponin, ng/dL	109.8 ± 146.1	67.2 ± 101.1	0.001	66.3 ± 117.5	67.3 ± 99.3	0.021
Brain Natriuretic Peptide, pg/dL	1109.0 ± 1194.9	511.3 ± 640.2	< 0.001	972.2 ± 1052.9	441.2 ± 517.6	< 0.001

Continuation

Medication and therapeutic strategy during hospitalization

iRAAS	59.5%	83.7%	< 0.001	78.8%	84.3%	0.090
Beta-blocker	34.2%	61.6%	< 0.001	48.7%	63.3%	0.002
Nitrates	39.2%	31.9%	0.392	28.3%	23.3%	0.082
Antiarrhythmics	21.8%	13.0%	0.038	19.5%	12.2%	0.025
Inotropes	53.2%	9.0%	< 0.001	10.6%	8.8%	0.316
Invasive strategy	54.0%	80.6%	< 0.001	56.2%	83.4%	0.001
Left Ventricular Ejection Fraction, %	40.7 ± 15.2	54.1 ± 12.0	< 0.001	50.1 ± 12.6	54.7 ± 11.8	0.001
Hospitalization days	5.6 ± 6	7.42 ± 4.8	< 0.001	9.2 ± 5.0	7.2 ± 4.8	< 0.001

Risk Scores

TIMI for STEMI	7 (5-9)	4 (2-6)	< 0.001	7 (4-8)	4 (2-6)	< 0.001
PURSUIT	15 (14-16)	12 (10-14)	< 0.001	14 (12-16)	12 (10-14)	< 0.001
SRI	38.9 (28.7-54.8)	25.2 (17.5 – 35.8)	< 0.001	36.2 (23.3-48.5)	24.2 (17.0-33.8)	< 0.001
GRACE	217 (195-249)	140 (109-171)	< 0.001	170 (142-194)	137 (107-167)	< 0.001
EMMACE	0.36 (0.23-0.55)	0.14 (0.06 – 0.31)	< 0.001	0.29 (0.13-0.48)	0.13 (0.05-0.28)	< 0.001
CHA ₂ DS ₂ -VAsC-HS	4 (3-5) 4.28 ± 1.6	4 (3-5) 3.73 ± 1.6	0.001	4 (3-5) 4.36 ± 1.8	4 (3-5) 3.7 ± 1.6	< 0.001
ACTION Registry–GWTG	58.5 (51-66)	33 (27 -42)	< 0.001	42 (33-50)	32 (26-41)	< 0.001
C-ACS	1 (1-2)	1 (1-1)	< 0.001	1 (1-2)	1 (1-1)	0.029
ProACS	5 (4-6)	2 (1- 3)	< 0.001	3 (2-4)	2 (1-3)	< 0.001

ACS: acute coronary syndrome; STEMI: ST-segment elevation myocardial infarction; NSTEMI/UA: non-ST-segment elevation myocardial infarction/ unstable angina; iRAAS: Renin angiotensin aldosterone system inhibitors; TIMI: Thrombolysis in Myocardial Infarction; PURSUIT: Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy; Simple Risk Index; GRACE: Global Registry of Acute Coronary Events; EMMACE: Evaluation of the Methods and Management of Acute Coronary Events; C-ACS: Canada Acute Coronary Syndrome. P-values obtained by the Mann-Whitney test for numerical variables and by chi-square or Fisher's exact test for categorical variables.

However, the ProACS and ACTION Registry–GWTG presented with a HL test p-value of 0.001 and < 0.001, respectively, indicating model lack of fit.

Regarding all-cause mortality and non-fatal ACS at one-year follow-up, all RS underperformed, with c-statistics consistently under 0.700. ProACS was only statistically superior to the C-ACS RS, which showed particularly poor discriminatory accuracy (c-statistic 0.550). Most RS revealed model lack of fit.

Discussion

Development of risks scores in acute coronary syndromes

Advances in medical therapy and the development of invasive strategies has had a significant impact on prognosis in ACS.¹⁻³ Risk stratification has become an essential part of the establishment of a personalized treatment strategy in patients with ACS, weighing the risks and benefits of an early invasive approach.^{1,2} In STEMI patients, primary percutaneous coronary intervention is the standard approach, thus early risk stratification is less important.^{1,3} However, risk stratification in STEMI still plays an important role in predicting which patients are at higher risk for mortality or recurrent ACS, thus warranting a more aggressive medical therapy.¹ Patients with NSTEMI/UA represent a much more heterogeneous group,

with early risk stratification playing a more central role in deciding which patients benefit more from an early invasive strategy.^{2-5,13} Several risk score have been formulated in the last 20 years, attempting to best predict which patients are at a higher risk for a worse outcome.³⁻¹³ The simple TIMI risk score for STEMI⁷ and for NSTEMI/UA¹³ was developed from large clinical trials, with controlled and selected populations. The TIMI RS for STEMI⁷ was formulated from the InTIME II trial which enrolled a total of 15,078 patients, all were candidates for fibrinolytic therapy. This risk score performed well at identifying high risk patients (c-statistics for predicting in-hospital mortality and in the first 24 hours after admission was 0.784 and 0.813, respectively).⁷ The TIMI for NSTEMI/UA was developed using the database of the TIMI 11B trial, with a total of 3910 patients, satisfactorily predicting all-cause mortality, myocardial infarction or urgent revascularization at 14 days.¹³ However, since it underperformed in our population, the authors decided not to use the RS. The SRI risk score was also calculated from the InTIME trial, using a cohort of 13,253 STEMI patients. This risk score satisfactorily predicted in-hospital death (c-statistic 0.79). The PURSUIT risk score was developed through the Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (eptifibatide) Therapy trial using a NSTEMI population of 9,461 patients, with a

Table 3 – Predictive accuracy and goodness of fit of the scores at predicting in-hospital mortality and comparison with the ProACS risk score

	In-hospital mortality				
	c-statistics (95% CI)	p-value	p-value (Hosmer–Lemeshow χ^2)	Comparing with the ProACS Risk Score	
				Δ	p-value
TIMI for STEMI	0.744 (0.695-0.792)	< 0.001	0.486	0.165	< 0.0001
PURSUIT	0.775 (0.733-0.817)	< 0.001	0.043	0.133	< 0.0001
SRI	0.732 (0.682-0.781)	< 0.001	0.23	0.176	< 0.0001
GRACE	0.890 (0.855-0.925)	< 0.001	0.298	0.0185	0.0879
EMMACE	0.749 (0.700-0.797)	< 0.001	0.566	0.160	< 0.0001
CHA ₂ DS ₂ -VAsC-HS	0.600 (0.543-0.656)	0.001	0.804	0.309	< 0.0001
ACTION Registry–GWTG	0.904 (0.870-0.938)	< 0.001	0.041	0.00399	0.6647
C-ACS	0.619 (0.554-0.684)	< 0.001	0.003	0.289	< 0.0001
ProACS	0.908 (0.876-0.941)	< 0.001	0.031	N/A	N/A

Δ : difference between the two AUC (area under the curve). TIMI: Thrombolysis in Myocardial Infarction; PURSUIT: Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy; Simple Risk Index; GRACE: Global Registry of Acute Coronary Events; EMMACE: Evaluation of the Methods and Management of Acute Coronary Events; C-ACS: Canada Acute Coronary Syndrome.

Table 4 – Predictive accuracy and goodness of fit of the scores at predicting in-hospital mortality and comparison with the ProACS risk score, in both STEMI and NSTEMI/UA

STEMI	In-hospital mortality				
	c-statistics (95% CI)	p-value	p-value (Hosmer–Lemeshow χ^2)	Comparing with the ProACS Risk Score	
				Δ	p-value
TIMI for STEMI	0.785 (0.720-0.849)	< 0.001	0.766	0.139	< 0.0001
PURSUIT	0.809 (0.758-0.861)	< 0.001	0.075	0.114	< 0.0001
SRI	0.781 (0.718-0.843)	< 0.001	0.011	0.143	< 0.0001
GRACE	0.899 (0.856-0.942)	< 0.001	0.603	0.0244	0.0331
EMMACE	0.795 (0.731-0.858)	< 0.001	0.392	0.129	< 0.0001
CHA ₂ DS ₂ -VAsC-HS	0.674 (0.596-0.751)	< 0.001	0.206	0.250	< 0.0001
ACTION Registry–GWTG	0.911 (0.874-0.948)	< 0.001	0.882	0.0127	0.2248
C-ACS	0.620 (0.531-0.708)	0.004	0.005	0.304	< 0.0001
ProACS	0.923 (0.892-0.955)	< 0.001	0.821	N/A	N/A

NSTEMI/UA	In-hospital mortality				
	c-statistics (95% CI)	p-value	p-value (Hosmer–Lemeshow χ^2)	Comparing with the ProACS Risk Score	
				Δ	p-value
TIMI for STEMI	0.696 (0.624-0.767)	< 0.001	0.377	0.202	< 0.0001
PURSUIT	0.742 (0.673-0.810)	< 0.001	0.551	0.157	< 0.0001
SRI	0.682 (0.604-0.761)	< 0.001	0.078	0.216	< 0.0001
GRACE	0.878 (0.822-0.934)	< 0.001	0.566	0.0205	0.2040
EMMACE	0.702 (0.629-0.774)	< 0.001	0.376	0.197	< 0.0001
CHA ₂ DS ₂ -VAsC-HS	0.534 (0.448-0.620)	0.453	0.455	0.364	< 0.0001
ACTION Registry–GWTG	0.895 (0.835-0.956)	< 0.001	< 0.001	0.00302	0.8411
C-ACS	0.618 (0.522-0.714)	0.009	0.077	0.281	< 0.0001
ProACS	0.898 (0.841-0.956)	< 0.001	0.001	N/A	N/A

Δ : difference between the two AUC (area under the curve). TIMI: Thrombolysis in Myocardial Infarction; PURSUIT: Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy; Simple Risk Index; GRACE: Global Registry of Acute Coronary Events; EMMACE: Evaluation of the Methods and Management of Acute Coronary Events; C-ACS: Canada Acute Coronary Syndrome.

Table 5 – Predictive accuracy and goodness of fit of the scores at predicting the occurrence of all-cause mortality and non-fatal ACS at one-year follow-up and comparison with the ProACS risk score

	All-cause mortality and non-fatal ACS at one-year follow-up				
	c-statistics (95% CI)	p-value	p-value (Hosmer–Lemeshow χ^2)	Comparing with the ProACS Risk Score	
				Δ	p-value
TIMI for STEMI	0.695 (0.650-0.741)	< 0.001	0.033	0.0323	0.0656
PURSUIT	0.682 (0.634-0.730)	< 0.001	0.001	0.0185	0.3846
SRI	0.680 (0.632-0.729)	< 0.001	0.042	0.0171	0.3854
GRACE	0.684 (0.639-0.729)	< 0.001	0.022	0.0209	0.1608
EMMACE	0.673 (0.623-0.723)	< 0.001	0.681	0.00997	0.6157
CHA ₂ DS ₂ -VAsc-HS	0.622 (0.570-0.673)	< 0.001	0.027	0.0414	0.2093
ACTION Registry–GWTG	0.690 (0.643-0.737)	< 0.001	0.005	0.0267	0.0567
C-ACS	0.550 (0.497-0.603)	0.057	0.366	0.113	0.0007
ProACS	0.663 (0.617-0.709)	< 0.001	0.015	N/A	N/A

Δ : difference between the two AUC (area under the curve). TIMI: Thrombolysis in Myocardial Infarction; PURSUIT: Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy; Simple Risk Index; GRACE: Global Registry of Acute Coronary Events; EMMACE: Evaluation of the Methods and Management of Acute Coronary Events; C-ACS: Canada Acute Coronary Syndrome.

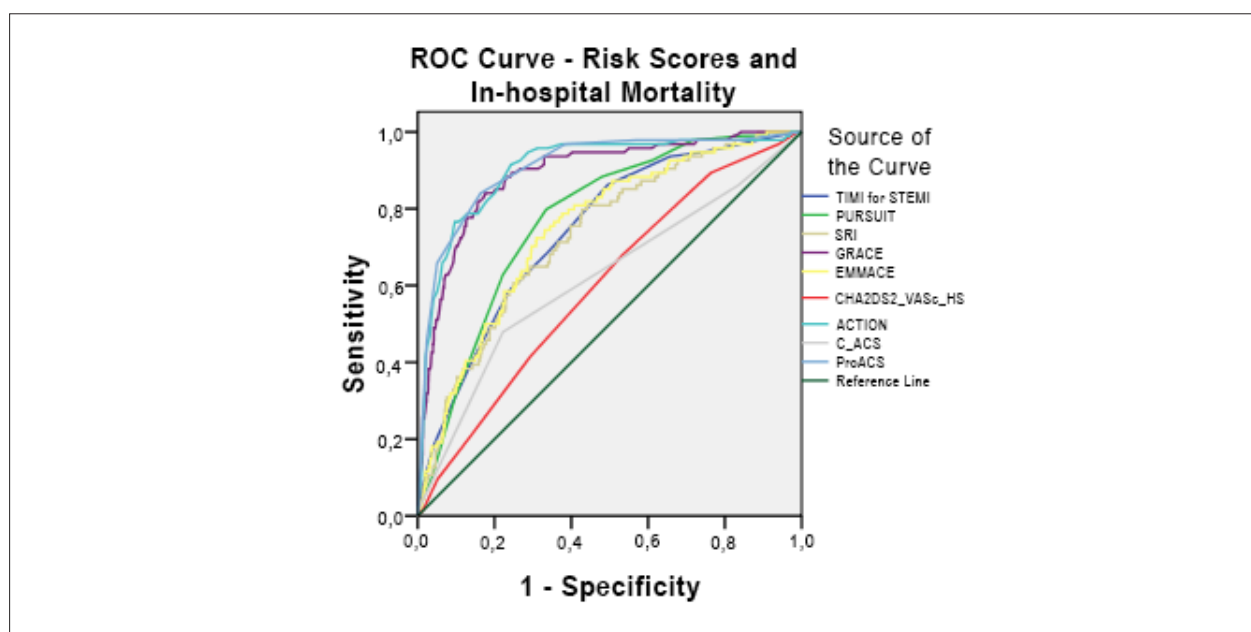


Figure 1 – Receiver operating characteristic (ROC) curves regarding risks scores and in-hospital mortality, in the total population. TIMI: Thrombolysis in Myocardial Infarction; PURSUIT: Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy; Simple Risk Index; GRACE: Global Registry of Acute Coronary Events; EMMACE: Evaluation of the Methods and Management of Acute Coronary Events; C-ACS: Canada Acute Coronary Syndrome.

c-statistic of 0.814. These RS are simple and intuitive, however, derivation from large trial databases tend to overlook specific high-risk patients.³⁻⁵ The GRACE risk score was developed using an international registry, much more representative of real-world patients, with a total of 11,389 patients enrolled.⁶ The GRACE risk score outperformed previous RS which tended to use clinical trial data. GRACE showed good predictive capacity for in-hospital mortality and at 6-month follow-up.^{6,17} This risk score was updated using

a cohort of 48,023 patients¹⁸ and has become the most widely used risk score both in STEMI and NSTEMI/UA.^{1,2} The EMMACE risk score was also developed from patients admitted for ACS over a 3-month period in 1995, compiling a total of 2,135 patients.⁹

A mathematical formula only comprising 3 variables (age, heart rate and systolic blood pressure) was formulated and revealed good performance at predicting mortality at 30 days (c-statistics of 0.76 to 0.79). This risk score is simple and reproducible.⁹

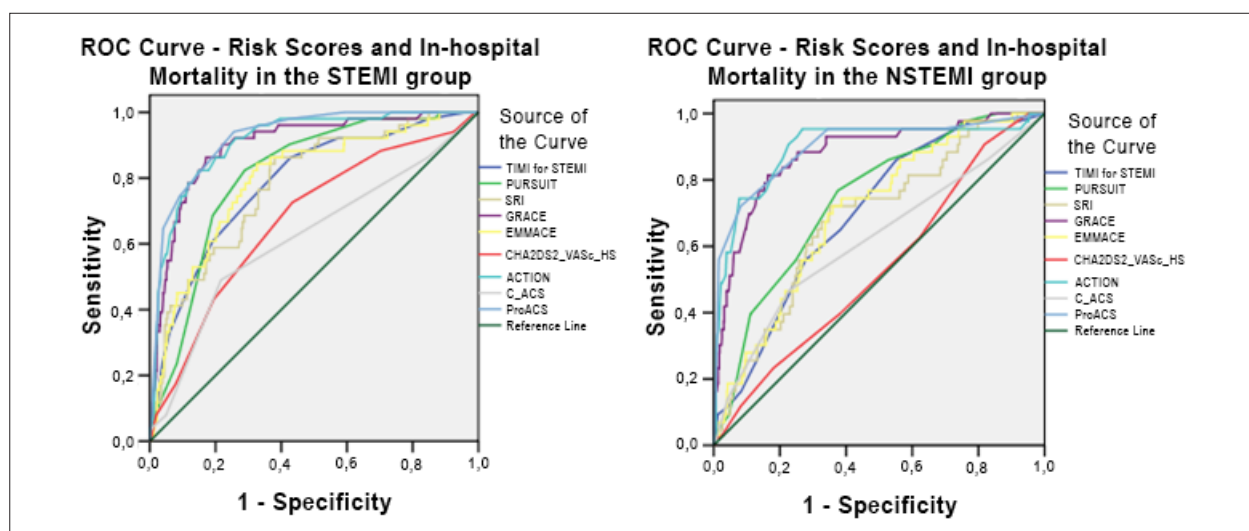


Figure 2 – Receiver operating characteristic (ROC) curves regarding risks scores and in-hospital mortality, in the STEMI and NSTEMI population individually. TIMI: Thrombolysis in Myocardial Infarction; PURSUIT: Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy; Simple Risk Index; GRACE: Global Registry of Acute Coronary Events; EMMACE: Evaluation of the Methods and Management of Acute Coronary Events; C-ACS: Canada Acute Coronary Syndrome.

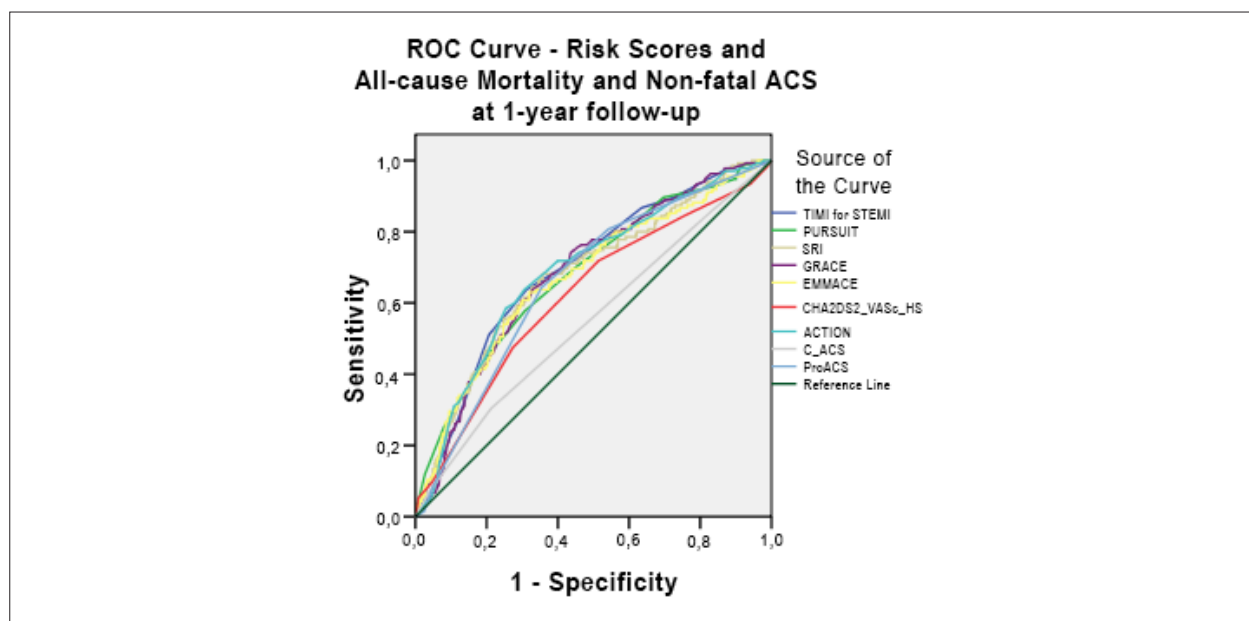


Figure 3 – Receiver operating characteristic (ROC) curves regarding risks scores and all-cause mortality and non-fatal ACS at one-year follow-up. TIMI: Thrombolysis in Myocardial Infarction; PURSUIT: Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy; Simple Risk Index; GRACE: Global Registry of Acute Coronary Events; EMMACE: Evaluation of the Methods and Management of Acute Coronary Events; C-ACS: Canada Acute Coronary Syndrome.

The Journal of the American College of Cardiology published in 2016 a new risk score.¹¹ This risk score was developed using data from the ACTION Registry–GWTG, which included a total of 145,952 patients from more than 300 hospitals from the United States of America admitted for both STEMI and NSTEMI.¹¹ The ACTION Registry–GWTG risk score performed well in the general population (c-statistic 0.88), as well as in specific subsets of patients.¹¹ This score appeared to be a good alternative to the GRACE score.

Finally, in 2017, the Portuguese Journal of Cardiology presented a new and simple risk score.³ The ProACS risk score, formulated by Timóteo et al.³ was developed using the Portuguese Registry of Acute Coronary Syndromes. The risk model was developed from the data of 17,380 patients. Internal and external validation of the score was done using 12,701 and 8,532 patients, respectively.³ Timóteo et al.³ built a simple risk score with only 4 variables, age, systolic blood pressure, Killip class and ST-segment elevation (information

easily obtainable even in a pre-hospital setting). The score performed well in predicting in-hospital mortality, both in STEMI and NSTEMI (c-statistics ranging from 0.785 to 0.809). This risk score was formulated similarly to the C-ACS, a score formulated by a Canadian group and published in the American Heart Journal. The C-ACS developed a simple score with 4 variables (age ≥ 75 , Killip class $> I$, systolic blood pressure < 100 mmHg and heart rate > 100 beats/min.¹⁰ The score was derived from the Acute Myocardial Infarction in Quebec (AMI-QUEBEC) and Canada ACS-1 registries, compiling a total of 6,182 patients.¹⁰ This score performed well at predicting worse outcome both in short-term (c-statistics ranging from 0.73 to 0.75) and in long-term mortality (c-statistics ranging from 0.73 to 0.76).¹⁰

It was the authors' objective to test several RS, which have been validated in the setting of ACS, to determine which one fared better at balancing a good predictive capability, combined with simple and intuitive use. The authors decided to apply the aforementioned RS in a single-centre population of patients admitted for ACS and compare each score to the ProACS.

Risk scores and in-hospital mortality

Almost all RS performed well. However, the CHA₂DS₂-VASC-HS and the C-ACS scores underperformed in this population (c-statistics of 0.600 and 0.619, respectively), even though both have been validated for the prediction of short-term mortality. The TIMI for STEMI, PURSUIT, SRI and EMMACE RS performed moderately well, with a c-statistics of 0.744, 0.775, 0.732 and 0.749, respectively. Of all the RS, three outperformed the other, achieving extremely good c-statistics, namely the ProACS, GRACE and ACTION Registry-GWTG RS. All of the RS predict short-term mortality. However, not all are equally efficient. The ProACS, GRACE and ACTION Registry-GWTG RS performed incredibly well when determining short-term mortality. A c-statistics of 0.908, 0.904 and 0.890 was calculated for each respective score. These results demonstrate a greater efficiency than that shown in previous studies.^{3,6,12,18} The ProACS demonstrated impressive results. It was significantly better than all the other RS, apart from the ACTION Registry-GWTG and GRACE RS. The only setback was a HL-test value of under 0.05 in both the ProACS and ACTION Registry-GWTG, indicating model lack of fit. This resulted from the presence of NSTEMI patients in the study.

All RS performed better at predicting in-hospital mortality in a STEMI setting. Again, the ProACS, ACTION Registry-GWTG and GRACE RS were the more accomplished RS, attaining c-statistics of 0.923, 0.911 and 0.899, respectively. These numbers are especially impressive since they outperformed each of their derivation and validation cohorts.^{3,12,18} ProACS demonstrated statistical superiority when compared to all others RS, apart from the ACTION Registry-GWTG and only marginal superiority when compared to the GRACE RS. In STEMI patients, these three RS revealed good fit. Once more, the TIMI for STEMI, PURSUIT, SRI and EMMACE RS had a satisfactory performance (c-statistics of 0.785, 0.809, 0.781 and 0.795, respectively). The CHA₂DS₂-VASC-HS and

the C-ACS RS performed disappointingly, with c-statistics of 0.674 and 0.620, respectively.

Concerning NSTEMI, the ProACS, GRACE and ACTION Registry-GWTG achieved a good predictive power, with c-statistics of 0.898, 0.878 and 0.895. In this particular population, both the ProACS and the ACTION Registry-GWTG showed lack of fit, thus interfering with the goodness of fit in the general population in these RS. The PURSUIT and EMMACE RS performed moderately good, with c-statistics of 0.742 and 0.702. It is impressive that the PURSUIT RS performed better at predicting a worse outcome in STEMI when compared to NSTEMI, since it is based upon NSTEMI patients.^{4,5} The TIMI for STEMI and SRI predictably underperformed (c-statistics of 0.696 and 0.682), since both were developed for STEMI patients.⁷ Again, the C-ACS revealed poor discriminatory accuracy (c-statistic 0.618) and the CHA₂DS₂-VASC-HS was unable to predict in-hospital mortality in NSTEMI patients (c-statistic of 0.534, $p = 0.453$).

Risk scores and long-term prognosis

The majority of the RS evaluated were developed solely for prediction of short-term prognosis.³⁻¹³ In this population, all the RS underperformed when predicting all-cause mortality and non-fatal ACS at one-year follow-up (c-statistics < 0.7). Almost all the RS presented with a c-statistic ranging from 0.622 to 0.690, without a statistically significant difference when compared with the ProACS. Notably, the C-ACS was unable to predict the worst long-term prognosis (c-statistic 0.550, $p = 0.057$), even though it was validated for long-term prognosis prediction.¹⁰ More studies are needed to develop RS with better discriminatory accuracy for predicting long-term prognosis in ACS patients.

Limitations

This is a single-centre retrospective, observational study of a small population. The analysis of the parameters was based on nonrandomized data. The population sample was relatively small and was composed by the sequential patients admitted in a single centralized hospital, thus it might represent a biased sample.

Conclusions

In this population, several RS showed good discriminatory accuracy at predicting short-term mortality. The ProACS, GRACE and ACTION Registry-GWTG RS performed incredibly, with c-statistics around 0.90. This revealed great predictive capability both in STEMI and NSTEMI patients. The TIMI for STEMI, PURSUIT, SRI and EMMACE RS performed moderately well. However, the CHA₂DS₂-VASC-HS²⁰ and the C-ACS underperformed, perhaps due to differences between the cohort from which they were based on and the population sample of this study. In this real-world population, it is evident that RS developed from databases of large registries, such as the GRACE, ProACS and the ACTION Registry-GWTG, seem to fare better than those derived from clinical trials. RS developed from clinical trials tend to include skewed

populations which avoid high-risk patients. None of the RS performed well at predicting long-term prognosis. This is understandable given they were intended for the prediction of short-term mortality.

The ProACS risk score proved to be an effective risk model, which performed incredibly well in this population, in both STEMI and NSTEMI patients. It is an intuitive risk score that requires only four easily obtainable variables. Its simplicity is rivalled only by the C-ACS, which has significantly underperformed in every aspect. The authors believe that ProACS is an appropriate and simple method to obtain adequate risk stratification regarding short-term prognosis that applies well to the Portuguese population.

Author contributions

Conception and design of the research: Gil J, Santos LF; Acquisition of data: Gil J, Abreu L, Antunes H, Gonçalves ML, Pires MI; Analysis and interpretation of the data: Gil J, Abreu L, Antunes H, Gonçalves ML, Pires MI, Santos LF, Henriques C, Matos A; Statistical analysis: Gil J, Henriques C, Matos A;

Writing of the manuscript: Gil J, Abreu L, Antunes H; Critical revision of the manuscript for intellectual content: Santos LF, Cabral JC, Santos JO.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39(2):119-77.
2. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37(3):267-315.
3. Timóteo AT, Aguiar Rosa S, Afonso Nogueira M, Belo A, Cruz Ferreira R; ProACS Investigators. ProACS risk score: An early and simple score for risk stratification of patients with acute coronary syndromes. *Rev Port Cardiol*. 2017;36(2):77-83.
4. de Araújo Gonçalves P, Ferreira J, Aguiar C, Seabra-Gomes R. TIMI, PURSUIT, and GRACE risk scores: sustained prognostic value and interaction with revascularization in NSTEMI-ACS. *Eur Heart J*. 2005;26(9):865-72.
5. Boersma E, Pieper KS, Steyerberg EW, Wilcox RG, Chang WC, Lee KL, et al. Predictors of outcome in patients with acute coronary syndromes without persistent ST-segment elevation. Results from an international trial of 9461 patients. The PURSUIT Investigators. *Circulation*. 2000;101(22):2557-67.
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. Morrow DA, Antman EM, Charlesworth A, Cairns R, Murphy SA, de Lemos JA, et al. TIMI risk score for ST-elevation myocardial infarction: A convenient, bedside, clinical score for risk assessment at presentation: An intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation*. 2000;102(17):2031-7.
8. Morrow DA, Antman EM, Giugliano RP, Cairns R, Charlesworth A, Murphy SA, et al. A simple risk index for rapid initial triage of patients with ST-elevation myocardial infarction: an InTIME II substudy. *Lancet*. 2001;358(9293):1571-5.
9. Dorsch MF, Lawrance RA, Sapsford RJ, Oldham J, Greenwood DC, Jackson BM, et al. A simple benchmark for evaluating quality of care of patients following acute myocardial infarction. *Heart*. 2001;86(2):150-4.
10. Huynh T, Kouz S, Yan AT, Danchin N, O'Loughlin J, Schampaert E, et al. Canada Acute Coronary Syndrome Risk Score: a new risk score for early prognostication in acute coronary syndromes. *Am Heart J*. 2013;166(1):58-63.
11. Cetin M, Cakici M, Zencir C, Tasolar H, Baysal E, Balli MC, et al. Prediction of coronary artery disease severity using CHADS2 and CHA2DS2-VASc scores and a newly defined CHA2DS2-VASc-HS score. *Am J Cardiol*. 2014;113(6):950-6.
12. McNamara RL, Kennedy KF, Cohen DJ, Diercks DB, Moscucci M, Ramee S, et al. Predicting In-Hospital Mortality in Patients With Acute Myocardial Infarction. *J Am Coll Cardiol*. 2016;68(6):626-35.
13. Antman EM, Cohen M, Bernink PJ, McCabe CH, Horacek T, Papuchis G, et al. The TIMI risk score for unstable angina/non-ST elevation MI. *JAMA*. 2000;284(7):835-42.
14. Santos JF, Aguiar C, Gavina C, Azevedo P, Morais J; Registo Nacional de Síndromes Coronárias Agudas da Sociedade Portuguesa de Cardiologia. Portuguese Registry of Acute Coronary Syndromes: seven years of activity. *Rev Port Cardiol*. 2009;28(12):1465-500.
15. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: a nonparametric approach. *Biometrics*. 1988;44(3):837-45.

16. Lemeshow S, Hosmer DW Jr. A review of goodness of fit statistics for use in the development of logistic regression models. *Am J Epidemiol*. 1982;115(1):92-106.
17. Eagle KA, Lim MJ, Dabbous OH, Pieper KS, Goldberg RJ, Van de Werf F, et al. A validated prediction model for all forms of acute coronary syndrome: estimating the risk of 6-month postdischarge death in an international registry. *JAMA*. 2004;291(22):2727-33.
18. Pieper KS, Gore JM, FitzGerald G, Granger CB, Goldberg RJ, Steg G, et al. Validity of a risk-prediction tool for hospital mortality: the Global Registry of Acute Coronary Events. *Am Heart J*. 2009;157(6):1097-105.
19. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137(2):263-72.
20. Taşolar H, Çetin M, Ballı M, Bayramoğlu A, Otlı YÖ, Türkmen S, et al. CHA2DS2-VASc-HS score in non-ST elevation acute coronary syndrome patients: assessment of coronary artery disease severity and complexity and comparison to other scoring systems in the prediction of in-hospital major adverse cardiovascular events. *Anatol J Cardiol*. 2016;16(10):742-8.



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

Is ProACS Score Just another Risk Stratification Score, or is it Ready for Implementation in Clinical Practice?

Ana Teresa Timóteo^{1,2} 

Departamento de Cardiologia - Hospital Santa Marta, Centro Hospitalar Universitário Lisboa Central,¹ Lisboa – Portugal

NOVA Medical School,² Lisboa – Portugal

Short Editorial related to the article: *Application of Risks Scores in Acute Coronary Syndromes. How Does ProACS Hold Up Against Other Risks Scores?*

Since the first publication of Framingham Risk Score in late 1950's, derived from data obtained in an observational study to investigate cardiovascular risk factors, several other risk scores were created around the globe and they have been increasingly popular particularly in the last 10-20 years in cardiovascular medicine. The objective of a risk score is to individualize the risk for an individual patient with the use of functional equations based on multiple risk factors. Patients at high risk should be submitted to specific interventions to improve outcome.

Despite this huge increase in risk scoring development, most have not been implemented in clinical practice. In fact, many models showed low predictive performance (as assessed by their calibration and discrimination) and some are poorly reported or were developed using inappropriate methods. For that reason, international guidelines were developed for adequate development and reporting of prediction models.¹ For that objective to be fulfilled, it should include an adequate selection of the development cohort, adequate methodology for selection of variables and an adequate validation, both internal and external. In fact, external validation is particularly important because it tests the performance of a prediction model in a different independent patient cohort, where they usually perform less well. It can also allow comparison with other risk stratification tools. This step is essential for safe implementation in clinical practice.

Risk stratification is important because populations are heterogeneous and present a large risk spectrum. Presently, there are very expensive and potent treatments, also with increased risk of adverse events, and thus, management decisions must be supported with risk stratification tools, although clinical judgment remains essential in these decisions. Unfortunately, in clinical practice, there is a misperception by the clinician that the use of individual risk indicators is sufficient to predict outcome and there is also a belief that the use of prediction rules may lead to overtreatment and that they are time

consuming.² This leads to the treatment–risk paradox that in many cases will result in inadequate treatment and poor outcome in patients at very high risk.

In this journal, Gil et al.³ present a paper where they compared several well-known risk stratification scores derived from both randomized clinical trial and registries.³ They also included some scores that were developed for other purposes of risk stratification in cardiovascular medicine. The scores that better predicted in-hospital mortality were GRACE, ACTION-Registry-GWTG and ProACS, but for long-term outcome, none of the studied scores was appropriate. This is a retrospective analysis performed in 1,452 patients admitted with an acute coronary syndrome (ACS), 45.1% with ST-elevation myocardial infarction, with in-hospital mortality of 6.5% and 9.9% of death / non-fatal ACS in a one-year follow-up.

ProACS risk score was developed with a very specific purpose of providing a very easy and simple risk score, with immediate variables, that could be applied early, in the first medical contact, to better decide on patient management strategy.⁴ ProACS was developed from one of the largest registries worldwide, the Portuguese Registry of Acute Coronary Syndromes, with more than 45,000 patients included.⁵ In the development study, this score showed good discrimination in all the study cohorts (development, internal and external validation), and similar results were also reported in an independent external validation cohort.^{4,6} Calibration was adequate in all these studies. Results were, however, slightly worst, compared to GRACE risk score and a recommendation was included that this should be used only as an early risk stratification score, with GRACE risk score to be used later after hospital admission. Surprisingly, in the present study, discrimination of ProACS was even high, with similar c-statistics when compared to the most potent risk stratification scores, but calibration was not adequate, particularly in the non-ST elevation ACS cohort.

One important finding is that ProACS risk score is very similar to C-ACS risk score;⁷ however, this one was developed in Canada with different patient characteristics, and had very low discrimination in the Portuguese population, stressing the importance of regional external validation studies. Also, risk scores developed from randomized clinical trials were less useful compared to risk scores developed from registries, in cohorts more representative of real-world populations. Clinical trials cohort is very selective, limiting extrapolation for general populations, patients are usually younger and healthier, with a lower rate of comorbidities and clinical trials do not reproduce practices and strategies used in most centres. For that reason, the external validity of models derived from clinical trials is usually lower, as we observed in the present study.

Keywords

Cardiovascular Diseases; Acute Coronary Syndrome; Propensity Score; Probability; Risk Factors; Prognosis.

Mailing Address: Ana Teresa Timóteo •

Hospital Santa Marta - Cardiology Department - Rua Santa Marta, 1110, Lisboa – Portugal

E-mail: ana_timoteo@yahoo.com

DOI: 10.5935/abc.20190122

The main objective of ProACS risk score is to immediately stratify the risk in patients with ACS to decide on the adequate management and thus its main objective is the short-term outcome. Results in longer-term follow up were not adequate. For long-term outcome, the inclusion of other variables, such as renal function, troponins and others are also important.

What should not be forgotten is that for each risk stratification score, impact studies should also be performed after external validation. In fact, external validity does not mean that beneficial clinical effects will be obtained when we use a risk score and it does not give information regarding the possible adverse events. Impact studies are essential

and should be studied separately from development and validation, preferably in randomized clinical trials and they are usually not performed. From the above, researchers should spend more time on validation and assessing the impact of existing models instead of developing more models that will most likely never be used in clinical practice. This should be the next step to definitely support the use of ProACS risk score in clinical practice.

From the results presented in this study, ProACS risk score will probably be soon implemented in clinical practice, due to the easy and simple application in clinical practice and high discrimination presented but impact studies are needed.

References

1. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariate prediction model for individual Prognosis or Diagnosis (TRIPOD): the TRIPOD statement. *Ann Intern Med.* 2015;162(1):55-63.
2. Eichler K, Zoller M, Tschudi P, Steurer J. Barriers to apply cardiovascular prediction rules in primary care: a postal survey. *BMC Fam Pract.* 2007 Jan 3;8:1
3. Gil J, Abreu L, Antunes H, Gonçalves ML, Pires MI, Santos LF, et al. Aplicação de escores de risco em síndromes coronárias agudas: como o ProACS se comporta diante de outros escores de risco? *Arq Bras Cardiol.* 2019; 113(1):20-30
4. Timóteo AT, Aguiar Rosa S, Afonso Nogueira M, Belo A, Cruz Ferreira R, ProACS Investigators. ProACS risk score: an early and simple score for risk stratification in patients with acute coronary syndromes. *Rev Port Cardiol.* 2017;36(2):77-83.
5. Timóteo AT, Mimoso J, em nome dos investigadores do Registo Nacional de Síndromes Coronárias Agudas. Portuguese Registry of Acute Coronary Syndromes (ProACS): 15 years of a continuous and prospective registry. *Rev Port Cardiol.* 2018;37(7):563-73.
6. Timóteo AT, Aguiar Rosa S, Nogueira MA, Belo A, Cruz Ferreira R. External validation of the ProACS score for stratification of patients with acute coronary syndromes. *Rev Port Cardiol.* 2016;35(6):323-8.
7. Huynh T, Kouz S, Yan AT, Danchin N, O'Loughlin J, Schamparet E, et al. Canada Acute Coronary Syndrome Risk Score: a new risk score for early prognostication in acute coronary syndromes. *Am Heart J.* 2013;166(1):58-63.



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

Serum Sirtuin 1, 3 and 6 Levels in Acute Myocardial Infarction Patients

Emrullah Kızıltunc,¹ Arzu Kösem,² Can Özkan,¹ Burcu Uğurlu Ilgin,³ Harun Kundi,^{1,4} Mustafa Çetin,¹ Ender Ornek¹

TC Sağlık Bakanlığı Ankara Numune Eğitim ve Araştırma Hastanesi - Cardiology,¹ Ankara – Turkey

TC Sağlık Bakanlığı Ankara Numune Eğitim ve Araştırma Hastanesi - Medical Biochemistry,² Ankara – Turkey

TC Sağlık Bakanlığı Gazi Mustafa Kemal Devlet Hastanesi – Cardiology,³ Ankara – Turkey

Beth Israel Deaconess Medical Center – Cardiology,⁴ Boston, Massachusetts – USA

Abstract

Background: Sirtuins may act in many cellular processes like apoptosis, DNA repair and lipid/glucose metabolism. Experimental studies suggested some sirtuin types may have protective effects against endothelial dysfunction, atherosclerosis, cardiac hypertrophy and reperfusion injury. Data about sirtuins in acute myocardial infarction (AMI) patients are scarce.

Objectives: To investigate temporal changes of serum sirtuin 1,3 and 6 levels in AMI patients; to compare the serum sirtuin 1,3 and 6 levels between AMI patients and control subjects; and to investigate the association of serum sirtuin 1,3 and 6 levels with prognostic markers of AMI.

Methods: Forty patients with AMI and 40 patients with normal coronary arteries were included. Left ventricular ejection fraction (LVEF), serum proBNP, CRP, sirtuin1, sirtuin 3 and sirtuin 6 levels were processed. Peak troponin T levels, GRACE score, first day / second day sirtuin levels were recorded of AMI patients. A p value < 0.05 was considered statistically significant.

Results: Serum sirtuin 1,3 and 6 levels in AMI patients were similar to those in normal coronary patients. No temporal change in serum sirtuin 1,3 and 6 levels were found in AMI course. No correlation was evident between the sirtuin levels and the following parameters: proBNP, CRP, peak troponin and LVEF. Baseline sirtuin 1 and 6 levels were positively correlated with reperfusion duration. Baseline sirtuin 3 levels were negatively correlated with GRACE score.

Conclusion: Serum sirtuin 1,3 and 6 levels in AMI patients were similar to those in normal coronary patients. This study does not represent evidence of the possible protective effects of sirtuin1, 3 and 6 in AMI patients. (Arq Bras Cardiol. 2019; 113(1):33-39)

Keywords: Sirtuins/drug effects; Atherosclerosis; Lipid Metabolism; Endothelium/dysfunction; Cardiomegaly; Cellular Senescence; Carcinogenesis

Introduction

Sirtuins are NAD (nicotinamide adenine dinucleotide) dependent enzymes which consist of seven members called Sirt 1-7.¹ The best known function of sirtuins is deacetylation, but they can also function as mono ADP ribosyltransferase, lipoamidase, demalonylase and desuccinylase.^{2,3} Sirtuins are involved in several biological processes like apoptosis, cellular survival, DNA repair/cellular aging and lipid/glucose metabolism.⁴ The information about the functions of sirtuins in carcinogenesis, aging and inflammation is also increasing.^{4,5} Additionally, there exist evidences that circulating sirtuin levels may associate with frailty, reduction of body fat mass or diabetes mellitus.⁶⁻⁸ Contemporary knowledge about the functions of sirtuins in the cardiovascular system in health

and disease states is also evolving. Recent experimental studies have demonstrated the possible role of sirtuins in various cardiovascular pathologies like cardiac hypertrophy, heart failure, endothelial dysfunction and atherosclerosis.^{9,10}

Survival of the acute myocardial infarction (AMI) patients have significantly improved with the advanced catheter-based therapies and increased availability of coronary care units, but this resulted increase in heart failure population.¹¹ Infarct size reduction is crucial to decrease the probability of clinical heart failure and to improve prognosis in AMI patients. Early reperfusion and reduction of reperfusion injury are basic management approaches to reduce the infarct size. However, there exist many variables ascertaining infarct size and only a little is known about the underlying sophisticated molecular mechanisms. Inflammation, thrombogenicity, and oxidative stress effect infarct size and prognosis.¹²⁻¹⁴ Experimental studies revealed that sirtuin 1, 3 and 6 have beneficial effects against atherosclerosis, dyslipidemia, oxidative stress, endothelial dysfunction and inflammation. In addition, sirtuin 1 and 3 may activate cardioprotective pathways in the setting of AMI.⁹ Therefore, serum sirtuin levels may associate with reduced myocardial infarct size and good prognostic markers in AMI patients. To the best of our knowledge, there is no data about the association between serum sirtuin 1,3 and 6 levels and prognostic markers of AMI patients in

Mailing Address: Emrullah Kızıltunc •

TC Sağlık Bakanlığı Ankara Numune Eğitim ve Araştırma Hastanesi - Cardiology
Talatpaşa Bulvarı, N° 44, Altındağ, Ankara 06100 – Turkey
E-mail: e.kiziltunc@gmail.com

Manuscript received August 21, 2018, revised manuscript October 25, 2018,
accepted November 01, 2018

DOI: 10.5935/abc.20190114

English-language literature. The goal of this pilot study is to investigate temporal changes of serum sirtuin 1,3 and 6 levels in AMI patients, to determine if there is any difference in serum sirtuin 1,3 and 6 levels between AMI patients and control subjects and to investigate the association between serum sirtuin 1,3 and 6 levels and prognostic markers of AMI patients like peak serum troponin levels, serum pro-BNP levels, GRACE score and post-MI LVEF.

Methods

The study protocol was approved by the local ethical committee and informed consent forms were obtained from all participants. We enrolled patients with acute ST-segment elevational MI (STEMI) and patients with normal coronary arteries in this cross-sectional study between June 2017 and November 2017. Patients with STEMI were diagnosed according to the third universal definition of myocardial infarction document.¹⁵ A primary percutaneous coronary intervention was performed and all of the STEMI patients received guideline-mediated medical therapy. GRACE risk score¹⁶ and TIMI risk score¹⁷ of the AMI patients were calculated. The duration between symptom onset to reperfusion, location of the infarction in electrocardiogram and presence of pre-infarction angina pectoris were recorded. Serum lipid levels, renal and hepatic function test results, complete blood count results, fasting blood glucose levels, and peak troponin T levels were also recorded. Serum C reactive protein levels and pro BNP levels were processed on the first day of ischemic insult in AMI patients. Venous samples were obtained at the admittance, 24th hour and 48th hour of the infarction for sirtuin 1,3 and 6 analysis to see whether there was any temporal change in serum sirtuin levels after myocardial infarction. Serum lipid levels, renal and hepatic function test results, complete blood count results and fasting blood glucose levels were obtained from local laboratory records and venous samples were collected for C reactive protein, pro BNP and sirtuin level analysis after the coronary angiography in normal coronary artery patients. Transthoracic echocardiography was performed and the LVEF, end diastolic diameter, septal and posterior wall thickness were recorded in all patients. All of the samples for sirtuin level analysis were centrifuged at 4000 rpm for 10 minutes, serums were separated and were frozen at -80 degrees Celsius. All sirtuin 1,3 and 6 levels were processed simultaneously with human sirtuin ELISA kits (YL Biotech, Shanghai, PRC).

Excluded from the study were as follows: The patients with a past history of MI, stable coronary artery disease, peripheral arterial disease, heart failure and any valvular heart disease, the patients with malignancy, active infection, any chronic inflammatory disease, and any chronic renal or hepatic disease.

Statistical analysis

SPSS 18.0 software for Windows (SPSS Inc. Chicago, IL) was used for analysis of data. For continuous variables, the normality of distribution was tested using Kolmogorov-Smirnov test. The results were presented as the mean $\pm$ standard deviation for variables with normal distribution and as median (interquartile range 25-75) for variables with abnormal distribution. The statistical comparisons of continuous variables were

performed using independent samples t-test or Mann-Whitney U test regarding the distribution pattern. The comparisons of categorical variables were performed using Chi-square test or Fisher's exact test. While investigating the association between sirtuins and prognostic markers of AMI, the correlation coefficients and their significance were calculated using the Spearman test. In AMI patients, serial serum sirtuin 1,3 and 6 levels were processed at the admittance, first day and the second day of the infarction and the Friedman test was conducted to test whether there was a significant temporal change in serum sirtuin levels in AMI patients. A p value < 0.05 was considered statistically significant.

Results

Forty consecutive STEMI patients and 40 consecutive control patients with normal coronary arteries were included into the study. Baseline clinical and laboratory characteristics of the patients were shown in table 1. White blood cell count, neutrophil count, serum creatinine, CRP, proBNP values and left ventricle mass index were significantly higher in the AMI group than in the control group. The control group was composed of more female patients and less smoking patients. The mean platelet count and the mean left ventricular ejection fraction were significantly higher in the control group than in the AMI group. There was no significant temporal change in serum sirtuin levels in AMI patients (Figure 1).

Clinical and laboratory features of AMI patients were shown in table 2. Fifteen patients experienced pre-infarction angina pectoris before the ischemic insult. Median peak troponin level was 41.6 ng/L in patients without pre-infarction angina and 28.2 ng/L in patients with pre-infarction angina (p = 0.202). Baseline serum sirtuin 1, 3 and 6 levels were similar in the patients with and without pre-infarction angina. No correlation was evident between baseline serum sirtuin levels and following parameters: CRP levels, peak troponin T levels, proBNP levels and LVEF. Baseline sirtuin 1 and 6 levels were positively correlated with reperfusion duration. On the other hand, baseline sirtuin 3 levels were significantly negatively correlated with GRACE score (Table 3).

Discussion

In this pilot study, we investigated serum sirtuin 1, 3 and 6 levels in AMI patients and patients with normal coronary arteries. We found that median serum sirtuin levels were similar in AMI patients and control patients. We observed that serum sirtuin levels did not show a significant temporal change in AMI course. There was no correlation between serum sirtuin levels and prognostic markers of AMI patients like peak troponin, proBNP, CRP and ejection fraction. Serum sirtuin 1 and 6 levels were positively correlated with reperfusion duration. In addition, we found a significant negative correlation between serum sirtuin 3 levels and GRACE score.

Atherosclerotic cardiovascular disease is the leading cause of death all over the world.¹⁸ Primary and secondary prevention attempts are evolving to decrease the global burden of this devastating disorder.¹⁹ Atherosclerosis pathogenesis is complicated and researches on the molecular basis of

Table 1 – Clinical and laboratory characteristics of the study patients

	Control patients n = 40	AMI patients n = 40	p Value
Age, y	59 ± 9	57 ± 14	0.481
Sex, Male, n(%)	23(57.5)	37(92.5)	< 0.001
Hypertension, n(%)	20(50)	14(35)	0.175
Smoking, n(%)	8(20)	27(67.5)	< 0.001
Diabetes Mellitus, n(%)	16(40)	11(27.5)	0.237
Family History for CAD, n(%)	4(10)	10(25)	0.077
Hyperlipidemia, n(%)	3(7.5)	5(12.5)	0.456
Fasting blood glucose, mmol/L	5.8(5.3-6.7)	5.9(5.4-8.2)	0.164
Creatinine, µmol/L	75 ± 16	84 ± 14	0.006
Total cholesterol, mmol/L	4.9 ± 1.0	4.8 ± 0.9	0.675
HDL, mmol/L	1.1 ± 0.3	1.0 ± 0.2	0.101
LDL, mmol/L	2.7 ± 0.9	2.9 ± 0.8	0.392
Triglyceride, mmol/L	4.3 ± 2.2	3.9 ± 2.2	0.385
Hemoglobin, gr/dl	14.6 ± 1.9	14.7 ± 1.8	0.904
Platelet count, *10 ³	279 ± 70	229 ± 52	0.001
WBC, *10 ³	8.5 ± 1.9	11.6 ± 3.1	< 0.001
Neutrophil count, *10 ³	5.1 ± 1.4	8.8 ± 3.1	< 0.001
Lymphocyte count, *10 ³	2.6 ± 0.9	2.0 ± 0.9	0.001
Monocyte count, *10 ³	0.8 ± 0.9	0.7 ± 0.3	0.581
CRP, nmol/L	28.5(9.5-57.1)	85.7(38.1-180.9)	< 0.001
proBNP, ng/L	48.8(24.2-113.0)	500.9(282.0-1309.0)	< 0.001
Sirtuins, ng/ml			
Sirtuin 1 basal	2.74(2.30-3.64)	2.53(2.06-3.21)	0.192
Sirtuin 1 first day	NA	2.24(1.89-2.89)	
Sirtuin 1 second day	NA	2.08(1.55-3.18)	
Sirtuin 3 basal	2.62(2.16-3.34)	2.40(1.29-3.29)	0.204
Sirtuin 3 first day	NA	2.46(1.37-2.97)	
Sirtuin 3 second day	NA	2.30(1.36-3.55)	
Sirtuin 6 basal	1.13(0.89-2.25)	1.00(0.78-1.37)	0.172
Sirtuin 6 first day	NA	1.16(0.87-1.56)	
Sirtuin 6 second day	NA	1.19(0.85-1.80)	
EF, %	64 ± 2	47 ± 8	< 0.001
LVMI, gr/m ²	87.3 ± 14.6	94.4 ± 16.3	0.044

Continuous variables were presented as mean ± standard deviation or medial (interquartile range 25-75) AMI: acute myocardial infarction; BNP: brain natriuretic peptide; CAD: coronary artery disease; CRP: c reactive protein; EF: ejection fraction; HDL: high density lipoprotein; LDL: low density lipoprotein; LVMI: left ventricle mass index. WBC: white blood cell count.

atherosclerosis proceed all over the world. In this context, this study evaluated the implication of serum sirtuin 1, 3 and 6 levels in AMI patients. Preliminary data about the sirtuins in cardiovascular diseases were obtained from experimental studies. It was demonstrated that sirtuin 1 exhibits antiatherogenic properties via acting on endothelium by endothelial nitric oxide synthase activation and reducing macrophage foam cell formation by nuclear factor κB inhibition.^{20,21} Another study showed that sirtuin 1 decrease

serum LDL cholesterol levels.²² It was found that sirtuin 1 have antithrombotic effect in addition to the other atheroprotective effects that were mentioned above.²³ Oxidative stress plays an important role in the pathogenesis of atherosclerosis and previous studies reported the antioxidant role of sirtuin 3.^{24,25} Sirtuin 6 has anti-inflammatory and LDL lowering features.^{26,27} Human data about sirtuins and cardiovascular disorders are limited. Gorenne et al.²⁸ reported that sirtuin 1 expression is reduced in human carotid atherosclerotic plaque.²⁸

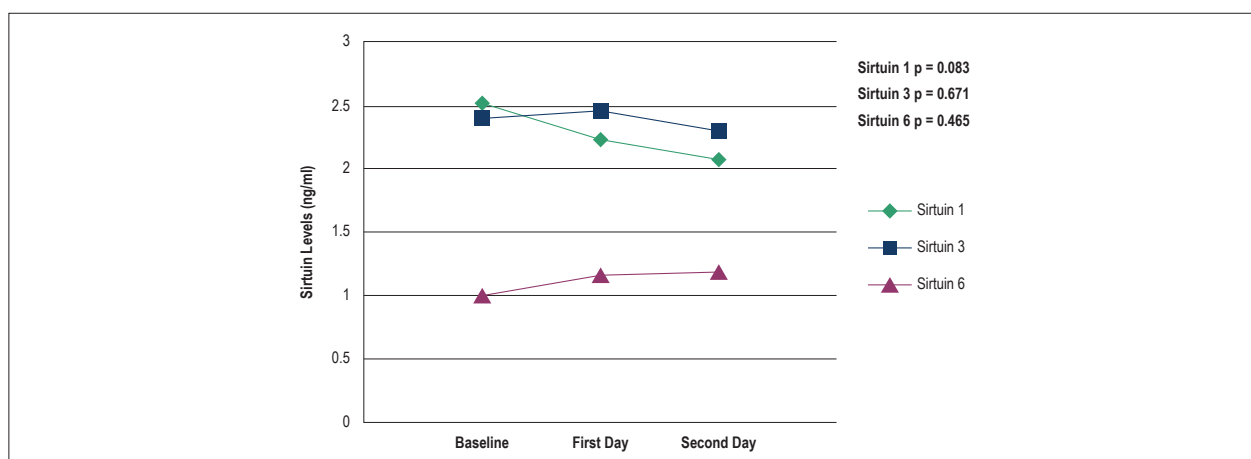


Figure 1 – Baseline, first day and second day median serum sirtuin levels of the acute myocardial infarction patients. Temporal changes of serum sirtuin 1,3 and 6 were statistically insignificant in acute myocardial infarction course.

Table 2 – Clinical and laboratory features of AMI patients (n = 40)

Presence of Pre-infarction Angina, n(%)	15(37.5)
Time to Perfusion (minutes)	225(120-300)
GRACE Score	
In hospital mortality	126(104-149)
6. month mortality	101(77-124)
In hospital MI/mortality	188(151-209)
6. month MI/mortality	148(121-167)
Killip Class	
1	38(95)
2	1(2.5)
3	1(2.5)
TIMI Risk Score	2(1-4)
Troponin T Levels(ng/L)	
Baseline	4.67(1.00-34.27)
First day	28.50(7.08-58.70)
Second day	14.11(6.46-39.95)
Peak	30.18(10.53-63.40)
MI Location n(%)	
Anterior	17(42.5)
Inferior	22(55)
Lateral	1(2.5)
Infarct Related Artery n(%)	
LAD	18(45)
Cx	3(7.5)
RCA	19(47.5)
Contrast Induced Nephropathy n(%)	4(10)

AMI: acute myocardial infarction; Cx: left circumflex artery; LAD: left anterior descending artery; MI: myocardial infarction; RCA: right coronary artery; TIMI: thrombolysis in myocardial infarction.

Breitenstein et al.²⁹ found that peripheral monocyte sirtuin 1 expression was lower in coronary artery disease patients compared to healthy subjects.²⁹ Judging by our results, this study may arise a debate about the protective functions of circulating sirtuin 1, 3 and 6 in cardiovascular disorders. The first issue is about the association between atherosclerosis and sirtuins. In our study population, median serum sirtuin 1, 3 and 6 levels did not significantly differ between the groups. According to our knowledge, this study is the first one comparing 'serum' sirtuin levels between normal coronary artery patients and AMI patients. There exist several studies evaluating sirtuin 1 levels in human atherosclerosis using different methodological manners. Breitenstein et al.²⁹ measured sirtuin 1 mRNA levels in peripheral monocytes and Gorenne et al.²⁸ measured sirtuin 1 mRNA and protein expression amount in human carotid endarterectomy materials.²⁸ While both of these studies found a negative association between atherosclerosis and sirtuin expression, Kilic et al.³⁰ found that serum sirtuin 1 levels were higher in stable CAD patients than in the control patients.³⁰

By taking all these data together, the causality between sirtuins and human atherosclerosis needs more investigation. Additionally, we firstly investigated the temporal change of serum sirtuin 1, 3 and 6 levels in the AMI course and did not found any significant change between admission, first and second day of AMI. Another issue needs to be addressed is the association between inflammation and sirtuin levels. In our study, serum sirtuin 1 and 3 levels were not correlated and serum sirtuin 6 levels were positively correlated with serum CRP levels, a widely accepted inflammatory marker. As we mentioned above, experimental studies suggested that sirtuins have anti-inflammatory effects and this is hypothesized as one of the mechanisms for atheroprotection.³¹ We expected to find a negative association between sirtuins and CRP, but the results were not concordant with our hypothesis. Although sirtuin 6 has an anti-inflammatory feature, a possible positive regulatory role for SIRT6 in the induction of pro-inflammatory cytokine expression is evident both in innate and adaptive immune cells. Thus our positive correlation finding between sirtuin 6 and CRP can be interpreted in this context.³²

Table 3 – Correlation analysis of prognostic variables of AMI patients with sirtuins

	Baseline Sirtuin 1	Baseline Sirtuin 3	Baseline Sirtuin 6
TIMI Score (Spearman's Rho/p)	0.109/0.508	-0.093/0.574	0.015/0.930
GRACE Score (Spearman's Rho/ p)			
In hospital mortality	-0.003/0.983	-0.478/0.002	-0.115/0.486
6. month mortality	-0.001/0.997	-0.351/0.028	-0.137/0.406
In hospital MI/mortality	0.045/0.785	-0.509/0.001	0.041/0.805
6. month MI/mortality	0.021/0.901	-0.501/0.001	-0.016/0.922
proBNP, (Spearman's Rho/ p)	0.294/0.073	-0.137/0.412	0.108/0.517
Peak Troponin T (Spearman's Rho/ p)	-0.107/0.518	-0.259/0.111	0.012/0.942
Time to Perfusion (Spearman's Rho/ p)	0.331/0.037	-0.249/0.121	0.312/0.050
CRP, (Spearman's Rho/ p)	0.312/0.053	-0.029/0.862	0.357/0.026
EF, (Spearman's Rho/ p)	-0.009/0.956	0.150/0.356	-0.132/0.419

AMI: acute myocardial infarction; BNP: brain natriuretic peptide; CRP: c reactive protein; EF: ejection fraction; TIMI: thrombolysis in myocardial infarction.

Our findings regarding the association between sirtuins and the parameters reflecting infarction size like peak troponin, ejection fraction and pro BNP levels were also remarkable. Opening the occluded artery and restoring the blood flow to the myocardium is the mainstay of the AMI management. However, it was suggested that restoration of blood flow may account for further myocardial damage and it is termed as reperfusion injury.³³ Microvascular obstruction, myocyte hypercontracture and contraction band necrosis, free radical generation and inflammatory cell accumulation are the proposed mechanisms for reperfusion injury.³⁴

Ischemic preconditioning, which reduces reperfusion injury can be defined as transient, sublethal ischemic episodes rendering the myocardium more resistant to a sustained, lethal ischemic period. Since first described by Murry et al.,³⁵ ischemic preconditioning has become the most relevant entity against reperfusion injury. Ischemic preconditioning requires complex intracellular molecular interactions and the molecular mechanism is still unclear.³⁶ It is suggested that some sirtuin types reduces ischemia reperfusion injury. In an experimental study, inhibition of sirtuin 1 resulted in reduction of bakuchiol induced cardioprotection in rat hearts.³⁷ Opening of the mitochondrial permeability transposition pores are crucial in the pathophysiology of ischemia reperfusion injury. Sirtuin 3 deacetylates the regulatory component of the mitochondrial permeability transposition pore and sirtuin 3 deficient mice myocytes exhibited an increase in mitochondrial swelling due to increase in the number of opened mitochondrial permeability transposition pores.³⁸ In this study, we investigated whether there was any association between serum sirtuin levels and infarct size markers. There was no correlation between serum sirtuin levels and peak troponin levels, LVEF and pro BNP levels in AMI patients. These findings reflect that serum sirtuin 1, 3 and 6 levels were not associated with the infarct size. Pre infarction angina pectoris can be used as the surrogate marker of ischemic preconditioning in daily practice and is associated with reduced peak troponin levels in AMI patients.³⁹ Although the number of subjects were low to make a firm conclusion, no difference was evident about serum sirtuin 1, 3 and 6 levels in the patients with and without pre infarction angina.

Finally, we should mention about the association between serum sirtuin 3 levels and GRACE score, and between reperfusion duration and serum sirtuin 1/6 levels. GRACE score is a well-known and validated risk score for morbidity and mortality in AMI patients.¹⁶ Although we could not find any correlation between serum sirtuin 3 levels and prognostic markers like peak troponin, pro-BNP and LVEF, the negative correlation between serum sirtuin 3 levels and GRACE score may be an inspiration for further studies to investigate the role of serum sirtuin 3 levels for the risk assessment in AMI patients. We found a positive correlation between serum sirtuin 1/sirtuin 6 levels and reperfusion duration. The duration between symptom onset and reperfusion was not a marker of mortality in STEMI patients.⁴⁰ Although correlated with reperfusion duration positively, sirtuin 1 and sirtuin 6 levels were not correlated with prognostic markers in AMI patients.

There are some limitations of our study. The small sample size seems the most important limitation of the study. The other important limitation is the methodological differences with previous studies. In previous studies, sirtuin analysis was performed with specimens from atherosclerotic plaques or peripheral mononuclear cells. Sirtuin mRNA levels and protein expression levels were evaluated in those studies. In our study, we directly measured serum sirtuin levels. Although our methodology was not the same with other studies, we firstly investigated serum sirtuin levels in our particular study population. This can be accepted as the originality of our study.

Conclusion

Serum sirtuin 1, sirtuin 3 and sirtuin 6 levels did not significantly differ between AMI patients and patients with normal coronary arteries. No temporal change was found in the serum levels of these sirtuins in the AMI course and there was no correlation between the serum levels of these sirtuins and the parameters reflecting myocardial infarct size like peak troponin level, LVEF and pro-BNP. We detected a negative correlation between sirtuin 3 and GRACE score, as a secondary finding. Cardioprotective role of serum sirtuin 1, 3 and 6 needs more investigation in AMI patients.

Author contributions

Conception and design of the research: Kızıltunç E, Kösem A, Çetin M, Ornek E; Acquisition of data: Kızıltunç E, Kösem A, Özkan C, İlgin BU, Kundi H; Analysis and interpretation of the data: Kızıltunç E, Kösem A, Kundi H, Çetin M, Ornek E; Statistical analysis: Kızıltunç E, Kundi H; Obtaining financing: Kızıltunç E, Özkan C, İlgin BU; Writing of the manuscript and Critical revision of the manuscript for intellectual content: Kızıltunç E, Kösem A, Özkan C, İlgin BU, Kundi H, Çetin M, Ornek E.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by Ankara Numune Training and Research Hospital.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Ankara Numune Training and Research Hospital under the protocol number E-17-1399. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

- Mei Z, Zhang X, Yi J, Huang J, He J, Tao Y. Sirtuins in metabolism, DNA repair and cancer. *J Exp Clin Cancer Res*. 2016;35(1):182.
- Du J, Zhou Y, Su X, Yu JJ, Khan S, Jiang H, et al. Sirt5 is a NAD-dependent protein lysine demethylase and desuccinylase. *Science*. 2011;334(6057):806-9.
- Mathias RA, Greco TM, Oberstein A, Budayeva HG, Chakrabarti R, Rowland EA, et al. Sirtuin 4 is a lipamidase regulating pyruvate dehydrogenase complex activity. *Cell*. 2014;159(7):1615-25.
- Schiedel M, Robaa D, Rumpf T, Sippl W, Jung M. The Current State of NAD(+)-Dependent Histone Deacetylases (Sirtuins) as Novel Therapeutic Targets. *Med Res Rev*. 2018;38(1):147-200.
- Carafa V, Rotili D, Forgione M, Cuomo F, Serrettiello E, Hailu GS, et al. Sirtuin functions and modulation: from chemistry to the clinic. *Clin Epigenetics*. 2016 May;8:61.
- Kumar R, Mohan N, Upadhyay AD, Singh AP, Sahu V, Dwivedi S, et al. Identification of serum sirtuins as novel noninvasive protein markers for frailty. *Aging Cell*. 2014;13(6):975-80.
- Mariani S, Fiore D, Persichetti A, Basciani S, Lubrano C, Poggiogalle E, et al. Circulating SIRT1 Increases After Intragastric Balloon Fat Loss in Obese Patients. *Obes Surg*. 2016;26(6):1215-20.
- Doulamis IP, Tzani AI, Konstantopoulos PS, Samanidis G, Georgiopoulos G, Toutouzas KP, et al. A sirtuin 1/MMP2 prognostic index for myocardial infarction in patients with advanced coronary artery disease. *Int J Cardiol*. 2017 Mar;230:447-53.
- Winnik S, Auwerx J, Sinclair DA, Matter CM. Protective effects of sirtuins in cardiovascular diseases: from bench to bedside. *Eur Heart J*. 2015;36(48):3404-12.
- Sosnowska B, Mazidi M, Penson P, Gluba-Brzozka A, Rysz J, Banach M. The sirtuin family members SIRT1, SIRT3 and SIRT6: Their role in vascular biology and atherogenesis. *Atherosclerosis*. 2017 Oct;265:275-82.
- Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39(2):119-77.
- Patel MR, Mahaffey KW, Armstrong PW, Weaver WD, Tasissa G, Hochman JS, et al. Prognostic usefulness of white blood cell count and temperature in acute myocardial infarction (from the CARDINAL Trial). *Am J Cardiol*. 2005;95(5):614-8.
- Hori M, Nishida K. Oxidative stress and left ventricular remodelling after myocardial infarction. *Cardiovasc Res*. 2009;81(3):457-64.
- Brown AJ, McCormick LM, Gajendragadkar PR, Hoole SP, West NE. Initial SYNTAX score predicts major adverse cardiac events after primary percutaneous coronary intervention. *Angiology*. 2014;65(5):408-12.
- Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33(20):2551-67.
- Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). *BMJ*. 2006;333(7578):1091.
- Morrow DA, Antman EM, Parsons L, de Lemos JA, Cannon CP, Giugliano RP, et al. Application of the TIMI risk score for ST-elevation MI in the National Registry of Myocardial Infarction 3. *JAMA*. 2001;286(11):1356-9.
- Gaziano JM. Global Burden of Cardiovascular Disease. In: Libby P, Bonow RO, Mann DL, Zipes DP (Ed). *Braunwald's Heart Disease*, 8 ed. Philadelphia: Elsevier; 2008. p.1-23.
- Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). *Atherosclerosis*. 2016 Sep;252:207-74.
- Zhang QJ, Wang Z, Chen HZ, Zhou S, Zheng W, Liu G, et al. Endothelium-specific overexpression of class III deacetylase SIRT1 decreases atherosclerosis in apolipoprotein E-deficient mice. *Cardiovasc Res*. 2008;80(2):191-9.
- Stein S, Lohmann C, Schäfer N, Hofmann J, Rohrer L, Besler C, et al. SIRT1 decreases Lox-1-mediated foam cell formation in atherogenesis. *Eur Heart J*. 2010;31(18):2301-9.

22. Miranda MX, van Tits LJ, Lohmann C, Arsiwala T, Winnik S, Tailleux A, et al. The Sirt1 activator SRT3025 provides atheroprotection in Apoe^{-/-} mice by reducing hepatic Pcsk9 secretion and enhancing Ldlr expression. *Eur Heart J*. 2015;36(1):51-9.
23. Stavrou EX, Fang C, Merkulova A, Alhalabi O, Grobe N, Antoniak S, et al. Reduced thrombosis in Klkb1^{-/-} mice is mediated by increased Mas receptor, prostacyclin, Sirt1, and KLF4 and decreased tissue factor. *Blood*. 2015;125(4):710-9.
24. Tao R, Coleman MC, Pennington JD, Ozden O, Park SH, Jiang H, et al. Sirt3-mediated deacetylation of evolutionarily conserved lysine 122 regulates MnSOD activity in response to stress. *Mol Cell*. 2010;40(6):893-904.
25. Sundaresan NR, Gupta M, Kim G, Rajamohan SB, Isbatan A, Gupta MP. Sirt3 blocks the cardiac hypertrophic response by augmenting Foxo3a-dependent antioxidant defense mechanisms in mice. *J Clin Invest*. 2009;119(9):2758-71.
26. Lappas M. Anti-inflammatory properties of sirtuin 6 in human umbilical vein endothelial cells. *Mediators Inflamm*. 2012 Oct;2012:597514.
27. Tao R, Xiong X, Depinho RA, Deng CX, Dong XC. FoxO3 transcription factor and Sirt6 deacetylase regulate low density lipoprotein (LDL)-cholesterol homeostasis via control of the proprotein convertase subtilisin/kexin type 9 (Pcsk9) gene expression. *J Biol Chem*. 2013;288(41):29252-9.
28. Gorenne I, Kumar S, Gray K, Figg N, Yu H, Mercer J, et al. Vascular smooth muscle cell sirtuin 1 protects against DNA damage and inhibits atherosclerosis. *Circulation*. 2013;127(3):386-96.
29. Breitenstein A, Wyss CA, Spescha RD, Franzeck FC, Hof D, Riwanoto M, et al. Peripheral blood monocyte Sirt1 expression is reduced in patients with coronary artery disease. *PLoS One*. 2013;8(1):e53106.
30. Kilic U, Gok O, Bacaksiz A, Izmirli M, Elibol-Can B, Uysal O. SIRT1 gene polymorphisms affect the protein expression in cardiovascular diseases. *PLoS One*. 2014;9(2):e90428.
31. Vachharajani VT, Liu T, Wang X, Hoth JJ, Yoza BK, McCall CE. Sirtuins Link Inflammation and Metabolism. *J Immunol Res*. 2016 Dec;2016:8167273.
32. Galli M, Van Gool F, Leo O. Sirtuins and inflammation: Friends or foes?. *Biochem Pharmacol*. 2011;81(5):569-76.
33. Kloner RA. Does reperfusion injury exist in humans? *J Am Coll Cardiol*. 1993;21(2):537-45.
34. Cannon RO. Mechanisms, management and future directions for reperfusion injury after acute myocardial infarction. *Nat Clin Pract Cardiovasc Med*. 2005;2(2):88-94.
35. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia: a delay of lethal cell injury in ischemic myocardium. *Circulation*. 1986;74(5):1124-36.
36. Heusch G. Molecular basis of cardioprotection: signal transduction in ischemic pre-, post-, and remote conditioning. *Circ Res*. 2015;116(4):674-99.
37. Feng J, Yang Y, Zhou Y, Wang B, Xiong H, Fan C, et al. Bakuchiol attenuates myocardial ischemia reperfusion injury by maintaining mitochondrial function: the role of silent information regulator 1. *Apoptosis*. 2016;21(5):532-45.
38. Hafner AV, Dai J, Gomes AP, Xiao CY, Palmeira CM, Rosenzweig A, et al. Regulation of the mPTP by SIRT3-mediated deacetylation of CypD at lysine 166 suppresses age-related cardiac hypertrophy. *Aging (Albany NY)*. 2010;2(12):914-23.
39. Kızıltunc E, Abaci A, Ozkan S, Alsancak Y, Unlu S, Elbeg S, et al. The Relationship between Pre-Infarction Angina and Serum Sphingosine-1-Phosphate Levels. *Acta Cardiol Sin*. 2014;30(6):546-52.
40. Cho YW, Jang JS, Jin HY, Seo JS, Yang TH, Kim DK, et al. Relationship between symptom-onset-to-balloon time and long-term mortality in patients with acute myocardial infarction treated with drug-eluting stents. *J Cardiol*. 2011;58(2):143-50.



Biomarkers in Acute Myocardial Infarction Diagnosis and Prognosis

Paula F. Martinez,¹ Silvio A. Oliveira-Junior,¹ Bertha F. Polegato,² Katashi Okoshi,² Marina P. Okoshi²

Instituto Integrado de Saúde, Universidade Federal de Mato Grosso do Sul,¹ Campo Grande, MS – Brazil

Faculdade de Medicina de Botucatu - Departamento de Medicina Interna - Universidade Estadual Paulista (UNESP),² Botucatu, SP – Brazil

Short Editorial related to the article: Serum Sirtuin 1, 3 and 6 Levels in Acute Myocardial Infarction Patients

Biomarkers have become a helpful tool for clinicians to establish acute and chronic diseases diagnosis and prognosis more accurately. The rapid expansion of researches in this field has been stimulated by molecular biology and omics techniques development.¹

In cardiovascular disease, the release of the intracellular components into the bloodstream in higher concentrations than usual are related to pathological conditions, such as necrosis, inflammation, hemodynamic stress, and thrombosis, and considered potential biomarkers.² Although a large number of cardiac biomarkers has been described, only a few of them were incorporated in clinical practice. Their usefulness depends on their specificity and sensitivity for detecting myocardial injury, reproducibility, accuracy, and the discriminatory limits to distinguish between pathologic from physiologic levels.²

Cardiac troponin (cTn) is a biomarker that has been established for diagnosis and that also provides robust prognostic information in acute myocardial infarction (AMI).¹ It is still the most recommended biomarker for detecting myocardial injury, especially due to its sensibility and specificity, even though it does not indicate the underlying etiology and pathophysiological mechanism.³ On the Fourth Universal Definition of Myocardial Infarction, myocardial infarction is defined when acute injury with abnormal cardiac biomarkers is detected (a rising and/or falling pattern of cTn values with at least one value above the 99th percentile upper reference limit) in association with evidence of acute myocardial ischaemia.³

Several other biomarkers representing different pathophysiological axes have been considered as a potential tool for diagnosis and risk stratification in AMI patients. These emerging biomarkers, including suppression of tumorigenicity 2 (ST2), galectin-3, copeptin, myeloperoxidase (MPO), high sensitivity C-reactive protein (CRP), pregnancy-associated plasma protein A (PAPP-A), growth-differentiation factor-15 (GDF-15), and others, have been studied individually or using a multimarker strategy.^{4,5} However, further studies are still required to determine their usefulness for AMI diagnosis and prognosis.

More recently, sirtuins have attracted great interest for their protective roles against inflammation, cancer, cardiovascular disease, vascular aging, and glucose homeostasis changes. Sirtuins were first discovered in the 1970s; their main action is the removal of acetylated groups from histone and non-histone proteins in the presence of nicotinamide adenine dinucleotide

(NAD⁺).⁶ Members of the sirtuin family are widely distributed throughout nature; this family has seven isoforms in the human body (Sirtuin1-7).⁷ Among sirtuins, the isoforms 1, 3, and 6 are the best characterized; they exert important effects in the cardiovascular system against atherosclerosis, myocyte hypertrophy, ischemia/reperfusion injury, oxidative stress, inflammation, and endoplasmic reticulum stress.⁸⁻¹⁰ Therefore, several studies have focused on the modulation of sirtuins with pharmacological and natural dietary compounds.⁹

In this issue of the Arquivos Brasileiros de Cardiologia, Kızıltunç et al.¹¹ published an interesting study in which they hypothesized serum sirtuin 1, 3 and 6 levels as possible biomarkers of myocardial infarct size and prognosis in AMI patients. Temporal levels of serum sirtuin 1, 3 and 6 and their association with AMI prognostic markers were examined. Patients with AMI (n = 40) and patients with normal coronary arteries (n = 40) were included and evaluated regarding left ventricular ejection fraction (LVEF), serum proBNP, CRP, and serum levels of sirtuin1, sirtuin 3, and sirtuin 6. Peak troponin T, GRACE score, and first day/second-day sirtuin levels were recorded for AMI patients. The authors found that sirtuin 1, 3 and 6 levels in AMI were similar to those in normal coronary patients, and no temporal change in sirtuins levels was observed during infarction course. Furthermore, there was no significant correlation between sirtuins levels and traditional markers of infarct size such as proBNP, peak troponin T, or LVEF. However, baseline sirtuin 1 and 6 levels were positively correlated with reperfusion duration, and baseline sirtuin 3 was negatively correlated with GRACE score. As pointed out by the authors, the negative correlation between sirtuin 3 and GRACE score suggests a possible role of sirtuin 3 for risk assessment in AMI patients.

In this study, it should be pointed out that 95% of AMI patients were classified as Killip I functional class. Therefore, although the authors have observed similar sirtuins levels in AMI and normal coronary patients, further investigation is needed to clarify whether serum sirtuin levels modify in AMI patients with worse cardiac function.¹²

In the literature, experimental artery occlusion-mediated infarction was combined with decreased sirtuin 3 expression in rats.¹³ Furthermore, sirtuin 3 knockout induced coronary microvascular dysfunction and cardiac remodeling impairment, while sirtuin 3 upregulation improved cardiac function in post-infarction mice.⁸ On the other hand, sirtuin 3 deficiency did not change infarction size or cardiac function.¹⁴ Therefore, additional studies are needed to clarify the role of sirtuins in the pathophysiology of myocardial infarction.

Keywords

Cardiovascular Diseases; Diagnosis; Prognosis; Mortality; Biomarkers; Sirtuins; Myocardial Infarction; Molecular Biology.

Mailing Address: Marina P. Okoshi •

Departamento de Clínica Médica, Faculdade de Medicina de Botucatu, UNESP. Rubião Junior, S/N. Postal Code 18.618-687 Botucatu, SP – Brazil
E-mail: marina.okoshi@unesp.br

DOI: 10.5935/abc.20190131

Acknowledgment

Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), process number 310876/2018-4 and 153424/2018-4).

References

1. Jaffe AS, Babuin L, Apple FS. Biomarkers in acute cardiac disease: The present and the future. *J Am Coll Cardiol*. 2006;48(1):1-11.
2. Thygesen K, Mair J, Katus H, Plebani M, Venge P, Collinson P, et al. Study Group on Biomarkers in Cardiology of the ESC Working Group on Acute Cardiac Care. Recommendations for the use of cardiac troponin measurement in acute cardiac care. *Eur Heart J*. 2010;31(18):2197-204.
3. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. ESC Scientific Document Group. Fourth universal definition of myocardial infarction (2018). *Eur Heart J*. 2019;40(3):237-69.
4. O'Donoghue ML, Morrow DA, Cannon CP, Jarolim P, Desai NR, Sherwood MW, et al. Multimarker risk stratification in patients with acute myocardial infarction. *J Am Heart Assoc*. 2016;5(5):e002586.
5. Wang YP, Wang JH, Wang XL, Liu JY, Jiang FY, Huang XL, et al. Roles of ST2, IL-33 and BNP in predicting major adverse cardiovascular events in acute myocardial infarction after percutaneous coronary intervention. *J Cell Mol Med*. 2017;21(11):2677-84.
6. Tang X, Chen XF, Wang NY, Wang XM, Liang ST, Zheng W, et al. SIRT2 acts as a cardioprotective deacetylase in pathological cardiac hypertrophy. *Circulation*. 2017;136(21):2051-67.
7. Wang Y, He J, Liao M, Hu M, Li W, Ouyang H, et al. An overview of sirtuins as potential therapeutic target: Structure, function and modulators. *Eur J Med Chem*. 2019;161:48-77.
8. Mihanfar A, Nejabati HR, Fattahi A, Latifi Z, Faridvand Y, Pezeshkian M, et al. SIRT3-mediated cardiac remodeling/repair following myocardial infarction. *Biomed Pharmacother*. 2018;108:367-73.
9. D'Onofrio N, Servillo L, Balestrieri ML. SIRT1 and SIRT6 signaling pathways in cardiovascular disease protection. *Antioxid Redox Signal*. 2018;28(8):711-32.
10. Zhang X, Ji R, Liao X, Castellero E, Kennel PJ, Brunjes DL, et al. MicroRNA-195 regulates metabolism in failing myocardium via alterations in sirtuin 3 expression and mitochondrial protein acetylation. *Circulation*. 2018;137(19):2052-67.
11. Kiziltunç E, Ozkan C. Serum Sirtuin 1,3 and 6 levels in acute myocardial infarction. *Arq Bras Cardiol*. 2019; 113(1):33-39.
12. Wu H, Cao G, Wang Y, Tian H, Du R. Increased serum CA125 and brain-derived neurotrophic factor (BDNF) levels on acute myocardial infarction: A predictor for acute heart failure. *Med Sci Monit*. 2019;25:913-9.
13. Klishadi MS, Zarei F, Hejazian SH, Moradi A, Hemati M, Safari F. Losartan protects the heart against ischemia reperfusion injury: Sirtuin3 involvement. *J Pharm Pharm Sci*. 2015;18(1):112-23.
14. Koentges C, Pfeil K, Meyer-Steenbuck M, Lothar A, Hoffmann MM, Odening KE, et al. Preserved recovery of cardiac function following ischemia-reperfusion in mice lacking SIRT3. *Can J Physiol Pharmacol*. 2016;94(1):72-80.



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

Readmission of Patients with Acute Coronary Syndrome and Determinants

Larissa Marina Santana Mendonça de Oliveira,¹ Ingrid Maria Novais Barros de Carvalho Costa,^{1,2} Danielle Góes da Silva,³ José Rodrigo Santos Santos Silva,⁴ José Augusto Soares Barreto-Filho,^{1,5,6} Marcos Antônio Almeida-Santos,⁷ Joselina Luzia Meneses Oliveira,^{1,5} Mirella Dornelas Batalha Moreira Buarque,^{8,9} Diva Aliete dos Santos Vieira,¹⁰ Antônio Carlos Sobral Sousa^{1,5,6}

Universidade Federal de Sergipe - Departamento de Pós-Graduação em Ciências da Saúde,¹ São Cristóvão, SE – Brazil

Instituto Federal de Educação Ciência e Tecnologia de Sergipe,² São Cristóvão, SE – Brazil

Universidade Federal de Sergipe - Departamento de Nutrição,³ São Cristóvão, SE – Brazil

Universidade Federal de Sergipe - Departamento de Estatística,⁴ São Cristóvão, SE – Brazil

Universidade Federal de Sergipe - Departamento de Medicina,⁵ São Cristóvão, SE – Brazil

Fundação São Lucas - Centro de Ensino e Pesquisa,⁶ Aracaju, SE – Brazil

Programa de Pós-graduação em Saúde e Ambiente da Universidade Tiradentes,⁷ Aracaju, SE – Brazil

Hospital do Coração,⁸ Aracaju, SE – Brazil

Fundação de Beneficência do Hospital Cirurgia,⁹ Aracaju, SE – Brazil

Universidade Federal de Sergipe - Departamento de Nutrição,¹⁰ Lagarto, SE – Brazil

Abstract

Background: Acute coronary syndrome (ACS) is responsible for high rates of hospital admission and readmission, which are associated with increased costs for the patient and the health system, and increased in-hospital mortality rates.

Objective: To evaluate readmission in patients with ACS and its determinants.

Methods: This was a retrospective cohort study of adult and elderly patients with ACS, readmitted to public and private referral cardiology hospitals within one year after the first hospitalization for ACS. The occurrence of readmissions, the time elapsed from the first to the second admission, and the use of medications at admission were collected from the medical records. Associations between categorical variables were evaluated by the chi-square test or the Fisher's exact test. Multiple logistic regression was used to evaluate predictors for readmissions. A $p < 0.05$ was set as statistically significant.

Results: Readmission rate was 21.5% ($n = 115$) and mean time between admissions was 122.7 ± 112.1 days. The patients were mostly men (64.0%), mean age of 63.15 ± 12.3 years. Among readmitted patients, 7% had a prognosis of "death", and 68.7% were readmitted more than once within a one-year period. The main reasons of readmission were cardiovascular diseases including ACS. Private health care and the diagnosis of congestive heart failure were associated with multiple logistic regression.

Conclusion: ACS was the main cause of readmission, with higher prevalence among users of supplemental health care. Readmissions were associated with previous diagnosis of congestive heart failure and the type of health care provided. (Arq Bras Cardiol. 2019; 113(1):42-49)

Keywords: Acute Coronary Syndrome; Hospitalization/economy; Patient Readmission/economy; Heart Failure; Delivery of Health Care/economy; Hospital Mortality; Socioeconomic Factors; Drug Therapy/economia.

Introduction

During the last years, there has been increasing rates of hospital admission and readmission for ischemic heart diseases, including acute coronary syndrome (ACS).¹ Hospital readmissions account for a significant increase in costs for the patient and public and private health system, and in

hospital mortality. The risk of death in readmitted patients is greater when readmissions occur for cardiac causes.²⁻⁴

After an ACS event, hospital readmissions may be associated with different cardiac conditions, including myocardial ischemia, arterial fibrillation and uncontrolled hypertension, and also non-cardiac conditions such as poor treatment adherence, alcohol consumption, psychological factors, socioeconomical factors and health system issues.⁵⁻⁷ Besides, hospital readmissions are correlated with the quality of the health care provided and management of comorbidities during hospitalization, and hence may be used as quality indicators of the healthcare services.^{8,9} The type of health care system can also influence readmission rates, as it reflects different levels of access to health care and inequality between individuals.⁸

Mailing Address: Larissa Marina Santana Mendonça de Oliveira •

Universidade Federal de Sergipe - R. Cláudio Batista, s/n - Palestina, Postal Code 49060-108, Aracaju, SE – Brazil, Aracaju, SE – Brazil

E-mail: nutrilarissamarina@gmail.com

Manuscript received August 09, 2018, revised manuscript October 23, 2018, accepted November 01, 2018

DOI: 10.5935/abc.20190104

Therefore, the present study aimed to evaluate readmission rates after an ACS event among users of a public, supplemental health care system in the state of Sergipe, Brazil, and to evaluate the association between readmission rate and socioeconomic determinants of lifestyle and clinical outcomes.

Methods

Study design

This was a retrospective cohort study of patients with ACS, conducted between August 2017 and April 2018. A total of 581 patients was selected during the first admission (October 2013–September 2015) to one of the four referral hospitals in the city of Aracaju, Brazil. Three of these institutions provided private health services and one of them provided public services. All participants were evaluated at three time points throughout the study: at hospital admission, and 30 days and 180 days after the ACS event.⁴

Clinical diagnosis of ACS at admission and the type of ACS – acute ischemia, acute myocardial infarction with ST-segment elevation (STEMI), and acute myocardial infarction without ST-segment elevation (NSTEMI) – were collected from medical records. These diagnoses were made based on physician's interpretation of symptoms (consistent with acute ischemia in the 24 hours prior to admission) and/or on elevation of biomarkers of cardiac ischemia, confirmed by electrocardiography, Doppler echocardiography or coronary cineangiography.

Once personal data (name, date of birth, date of hospital admission) of patients were obtained, the medical records were searched for the occurrence of readmissions within one year after the first admission for ACS.

Study sample

One-year readmission after first hospitalization for ACS was investigated in a cohort of 581 patients with ACS (Figure 1).

Inclusion criteria

All patients admitted for ACS in cardiology referral hospitals in Aracaju, Sergipe, Brazil, identified at baseline of the study were included.

Exclusion criteria

Patients who died during or after discharge of the first hospitalization, patients who were not readmitted after discharge of the first admission, and those who were presented readmission with less than 24 hours of hospital stay.

Outcome measures

Socioeconomic status

Patients' personal data were retrieved from the database of first admitted ACS patients during the period from October 2013 to September 2015.⁴ A semi-structured questionnaire was used at the time of admission for ACS. Data of age (adults and elderly patients), sex (female and male), self-referred race (white, pardo, black), educational attainment (more or less 9 years of schooling), per capita income (less than 1 salary/person, 1-3 salaries/person, 3-5 salaries/person and more than 5 salaries/person), type of health care (public or private), life habits – alcohol consumption and smoking, reported by the patient or caregiver, and physical activity (classified by the international physical activity questionnaire, IPAQ) – nutritional status according to the body mass index (BMI) and waist circumference (WC). BMI was classified into low weight, normal weight and overweight, according to the World Health Organization (WHO)¹⁰ cut-off points (for adults) and the Pan American Health Organization (PAHO)¹¹ cut-off points (for older patients). A WC < 80 cm for women and < 94 cm for men was considered normal.¹⁰

Hospital readmission

Occurrence of readmissions within one year after discharge was searched in the medical records of four cardiology referral hospitals. Data regarding the cause and date of readmissions and use of medications at the time of readmission were collected. All this information was transferred into a structured questionnaire.

Hospital admissions were categorized according to the primary diagnosis and the reason of admission – ACS, cardiovascular and noncardiovascular causes.

Drug therapy

After 30 and 180 days after discharge, the use, or not, of the following drugs was assessed: antiplatelet agents, statins,

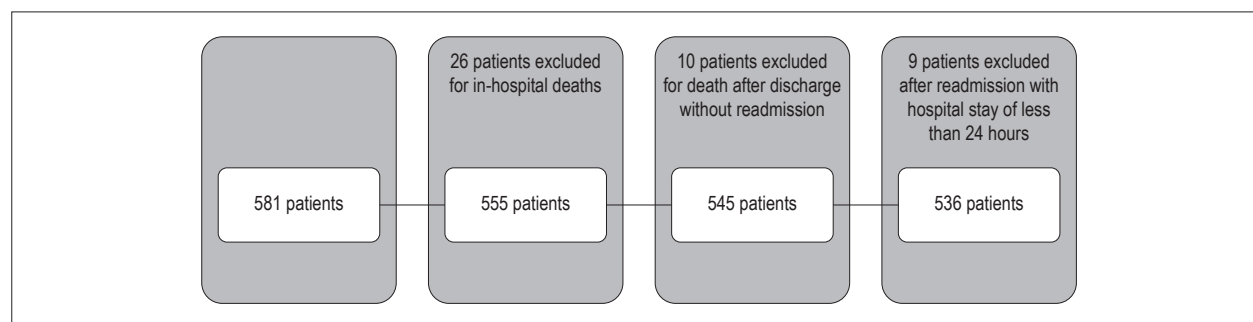


Figure 1 – Flow chart of the occurrence of readmission within one year after the first admission in patients with acute coronary syndrome.

beta blockers, angiotensin-converting enzyme inhibitors (ACEI), and angiotensin receptor blockers (ARBs). The use of these medications at home was also evaluated at readmission (collected from the medical records).

Physical activity

The practice of physical activity was evaluated using the short version of the IPAQ.^{12,13} This instrument classifies the patient into four categories, based on the intensity levels of physical activity: very active, active, insufficiently active and inactive. In our study, "very active" and "active" individuals according to the IPAQ were considered "active", and those classified as "insufficiently active" and "inactive" in the IPAQ were considered "inactive". The level of physical activity at hospital admission, and 30 days and 180 days after discharge was assessed by telephone.

Clinical features

We evaluated the type of ACS at first admission, and the presence of previous systemic arterial hypertension (SAH), diabetes mellitus (DM), dyslipidemias, coronary artery disease (CAD), congestive heart failure, angina, AMI, angioplasty, myocardial revascularization and chronic kidney disease. All variables were categorized into present or absent (yes or no).

Statistical analysis

Categorical variables were expressed as absolute and relative frequency, and distribution of quantitative variables was tested for normality using the Kolmogorov-Smirnov test. Variables that met the assumption of normality were presented as mean and standard deviation. Associations between categorical variables were assessed using the chi-square test or the Fisher's exact test, as appropriate. A $p < 0.05$ was set as statistically significant; all variables with $p < 0.20$ after association test and those that were risk factors for cardiovascular diseases were subjected to multiple logistic regression analysis.

Fourteen variables— sex, type of health care, race, age, hypertension, dyslipidemia, DM, congestive heart failure, use of statins on day 180, educational attainment, smoking, alcohol consumption, type of ACS – were selected as independent variables in the regression model, and readmission as dependent variable. The odds ratio (OR) and 95% confidence interval was used in the model. The Hosmer-Lemeshow goodness of fit test was used to evaluate the fitness of the model.

All analyses were performed using the R software, version 3.4.0 (The R Core Team, 2016).¹⁴

Results

A total of 536 patients were considered eligible for the study. Mean age was 63.15 ± 12.26 years, and most of the were men (64.0%). One hundred fifteen readmitted patients were identified (21.5%). Readmissions occurred 122.74 ± 112.14 days after discharge from the first hospitalization. Among readmitted patients, 7% had the

prognosis of "death", and 68.7% were readmitted more than once within a one-year period.

Regarding the reasons of hospital readmissions, 42.6% were ACS, 20.9% other cardiovascular causes (pulmonary hypertension, peripheral obstructive disease, second-degree atrioventricular block, and mitral insufficiency) and 36.52% other noncardiovascular causes (malnutrition, respiratory insufficiency, kidney disease, DM and complications, unspecified disorder of vestibular function, diverticulitis, hernioplasty, trauma and hyponatremia).

Table 1 presents the association of readmission with socioeconomic variables with the type of health care provided, nutritional status and life style. White patients, patients with higher educational attainment, those with higher family income and users of private health care services showed higher readmission rates.

Regarding clinical conditions associated with readmission (Table 2), readmission rates were higher in patients with STEMI, dyslipidemias, chronic kidney disease, congestive heart failure, angina, AMI, and previous angioplasty.

With respect to the use of medications after hospital discharge (Table 3), only absence of statin 180 days after the ACS event was associated with hospital readmission.

Factors associated with readmission were subjected to multiple logistic regression analysis (Table 4). Type of health care and congestive heart failure showed statistical significance. Users of private health care services had higher odds of rehospitalization than those attending public health clinics. However, patients with previous congestive heart failure had 1.81 times greater odds of readmissions.

Discussion

The readmission rate of 21.46% found in the present study was similar to that (24.5%) reported in the study by Dreyer et al.,¹⁵ who evaluated the rate of readmissions in 3,536 patients within one year after AMI in the USA. A study conducted in Canada with 3,411 patients of both sexes reported a higher readmission rate (61.7%) in one year after first hospitalization for ACS.⁷

Rehospitalization rates in our study were also lower than those reported by Ricci et al.(47.9%),⁸ evaluating 30-day readmission in a complex care hospital. Sangu et al.¹⁶ believe that readmission rates can be influenced by the time period of evaluation following discharge. Readmission rates can also be affected by geographic factors in a population.¹⁷

Readmission rate is also a predictor of the performance of hospital activities and the occurrence of complications after discharge,¹⁸ which can reflect the accessibility to primary health care services. Self-referral to hospitals may be explained by a difficult access to primary care services, and the idea of a treatment focused on acute rather than chronic care, which raises self-referral to complex care hospitals.^{19,20}

Readmission rates, however, are not always associated with the access to health care centers and quality of care provided. The rates may be associated with complexity of disease and patients' individual features, including socioeconomic status and disease severity. On the other hand, planned readmissions have been associated with the quality of hospital care.^{21,22}

Table 1 – Socioeconomic data, nutritional status, lifestyle habits, and type of health care provided associated with readmission in patients with acute coronary syndrome in Aracaju, Brazil, 2017

Variable (%)	Readmission		p value*
	Yes	No	
Socioeconomic variables			
Sex			
Female	49 (25.39%)	144 (74.61%)	0.1201
Male	66 (19.24%)	277 (80.76%)	
Race			
White	55 (29.73%)	130 (70.27%)	0.0008
Black/pardo	54 (16.67%)	270 (83.33%)	
Educational attainment			
< 9 years	44 (16.18%)	228 (83.82%)	0.0035
≥ 9 years	71 (26.89%)	193 (73.11%)	
Family income (per capita)			
≤ 1 salary/person	12 (12.63%)	83 (87.37%)	0.0022
> 1 salary and ≤ 3 salaries/ person	20 (14.93%)	114 (85.07%)	
> 3 salaries e ≤ 5 salaries/ person	29 (23.97%)	92 (76.03%)	
> 5 salaries/ person	53 (29.12%)	129 (70.88%)	
Age group			
Adults	35 (16.99%)	171 (83.01%)	0.0599
Elderly	80 (24.24%)	250 (75.76%)	
Nutritional status			
BMI			
Low weight	6 (18.18%)	27 (81.82%)	0.8271
Normal weight	48 (22.43%)	166 (77.57%)	
Overweight	60 (20.91%)	227 (79.09%)	
Abdominal circumference			
Inadequate	83 (20.75%)	317 (79.25%)	1.0000
Adequate	27 (21.09%)	101 (78.91%)	
Lifestyle habits			
Physical activity at admission			
Inactive	66 (23.08%)	220 (76.92%)	0.3828
Active	49 (19.6%)	201 (80.4%)	
Physical activity 30 days after admission			
Inactive	89 (20.37%)	348 (79.63%)	0.6298
Active	11 (16.92%)	54 (83.08%)	
Physical activity 180 days after admission			
Inactive	62 (22.55%)	213 (77.45%)	0.2203
Active	36 (17.56%)	169 (82.44%)	
Alcohol consumption			
Yes	15 (22.06%)	53 (77.94%)	1.0000
No	100 (21.37%)	368 (78.63%)	
Smoking			
Yes	17 (18.89%)	73 (81.11%)	0.6105
No	98 (21.97%)	348 (78.03%)	
Type of health care			
Private	89 (29.47%)	213 (70.53%)	< 0.0001
Public	26 (11.11%)	208 (88.89%)	

*Chi-square test

Table 2 – Clinical conditions associated with readmissions in patients with acute coronary syndrome in Aracaju, Brazil, 2017

Variable	Readmission		p value*
	Yes	No	
Type of ACS			
Unstable angina	20 (20.83%)	76 (79.17%)	0.0205
NSTEMI	56 (27.45%)	148 (72.55%)	
STEMI	39 (16.53%)	197 (83.47%)	
Arterial hypertension	97 (22.99%)	325 (77.01%)	0.1255
Dyslipidemias	81 (27.93%)	209 (72.07%)	0.0001
Diabetes mellitus	48 (25.81%)	138 (74.19%)	0.0933
Previous CAD	59 (30.73%)	133 (69.27%)	0.0001
Congestive heart failure	39 (31.45%)	85 (68.55%)	0.0030
Angina	66 (25.38%)	194 (74.62%)	0.0408
Previous AMI	58 (30.53%)	132 (69.47%)	0.0002
Previous angioplasty	31 (32.29%)	65 (67.71%)	0.0066
Previous myocardial revascularization	12 (31.58%)	26 (68.42%)	0.1700
Previous chronic kidney disease	18 (51.43%)	17 (48.57%)	< 0.0001

*ACS: acute coronary syndrome; NSTEMI: acute myocardial infarction without ST-segment elevation (NSTEMI); STEMI: acute myocardial infarction with ST-segment elevation (STEMI); AMI: acute myocardial infarction; CAD: coronary artery disease; Chi-square test.

Table 3 – Drug therapy associated with readmissions in patients with acute coronary syndrome in Aracaju, Brazil, 2017

Variable	Readmission		p value*
	Yes	No	
Without ASA for 30 days	3 (15.8%)	16 (84.2%)	1.0000
Without antiplatelet agents for 30 days	9 (30.0%)	21 (70%)	0.2111
Without statin for 30 days	6 (11.5%)	46 (88.5%)	0.2037
Without β -blockers for 30 days	12 (35.3%)	22 (64.7%)	0.0507
Without ACEI and/or ARBs for 30 days	6 (15.0%)	34 (85.0%)	0.4259
Without ASA for 180 days	5 (14.3%)	30 (85.7%)	0.4566
Without antiplatelet agents for 180 days	9 (16.4%)	46 (83.6%)	0.5640
Without statin for 180 days	8 (10.3%)	70 (89.7%)	0.0293
Without β -blockers for 180 days	12 (24.5%)	37 (75.5%)	0.6863
Without ACEI and/or ARBs for 180 days	16 (24.6%)	49 (75.4%)	0.5628

* acetylsalicylic acid (ASA); ACEI: angiotensin-converting enzyme inhibitors; ARBs: angiotensin receptor blockers; chi-square test or Fisher's exact test

The presence of other risk factors, particularly concomitant ones, increases the odds of readmission.²³ The occurrence of comorbidities associated with ACS affects disease severity, and increases the need for invasive interventions. A study conducted by Belitardo & Ayoub,¹ that evaluated readmission in elderly patients, reported that SAH, sedentary lifestyle, dyslipidemia, DM, stress, smoking and obesity increased the odds of requiring invasive procedures and readmissions.

Patient destination after discharge, which is related to disease severity, is also associated with 30-day readmission in patients with congestive heart failure, as discussed in the study by Mirkin et al.²⁴ Patients had different destinations after

discharge, and those requiring specialized support services had higher readmission rates.

The diversity of causes of readmission reinforces the importance of the access to regional health services and the degree of coverage of health services to reduce risk factors and complications that may affect readmission outcomes.²⁵

Therefore, strategies aimed at reducing the occurrence of readmission should include planning of discharge, promotion of health education of patients and family members, scheduling of patients' follow-up before and after discharge, appropriate use of medications, effective communication

Table 4 – Multiple logistic regression of variables in patients with acute coronary syndrome in Aracaju, Brazil, 2017

Variables	OR (95%CI)	p value
Male sex	0.78 (0.45; 1.38)	0.396
Public health care	0.46 (0.21; 0.98)	0.048
Elderly patients	1.11 (0.63; 1.99)	0.718
Black/pardo race	0.58 (0.34; 1.00)	0.050
Hypertension	1.72 (0.85; 3.73)	0.149
Dyslipidemia	1.69 (0.96; 3.04)	0.073
Diabetes mellitus	0.92 (0.53; 1.56)	0.749
Congestive heart failure	1.81 (1.01; 3.21)	0.042
Without statin for 180 days	0.76 (0.31; 1.70)	0.526
High school/higher education	1.56 (0.87; 2.85)	0.140
Smoking	1.43 (0.65; 2.99)	0.356
Alcohol consumption	1.93 (0.86; 4.22)	0.102
STEMI	1.30 (0.67; 2.61)	0.445
NSTEMI	0.97 (0.45; 2.13)	0.943

OR: Odds Ratio; STEMI: acute myocardial infarction with ST-segment elevation (STEMI); NSTEMI: acute myocardial infarction without ST-segment elevation (NSTEMI)

between patients and healthcare staff at discharge and between the hospital and follow-up care.²⁶

The present study showed that users of private health services showed higher odds of readmissions as compared with those attending public healthcare facilities. Also, the study showed an association between having access to private health services and the capacity of having health insurance. Thus, the type of health care is related to patients' socioeconomic status, race, educational attainment, family income and older age.²⁷ In addition, the income may be associated with educational attainment, which indicates that people with higher education attainment have higher income and greater odds to have access to private health services. Therefore, users of health insurance plans have greater access to a high variety of health services,^{2,28} and an increase in the income is slightly associated with increasing acquisition of health insurance plans.

According to a Brazilian household budget survey (POF, Pesquisa de Orçamentos Familiares) conducted in 2008-2009,²⁹ households spent an average of 5.9% of the family income with health care, including medications and health plans.^{27,29}

A Brazilian nation-wide study by Malta et al.²⁷ reported that in general, users of private health services are mostly women, white patients. Also, the use of health insurance plans is associated with socioeconomic status, reflected as race, educational attainment, family income and older age.

On the other hand, the public system is characterized by a difficult access to treatment, including invasive therapies such as myocardial reperfusion and medical treatment. Also, due to improvements in notification and classification of these events, complex cases are prioritized to hospitalizations.^{30,31} These findings corroborate previous results showing higher readmission rates in private health facilities than public ones.

The main reasons of readmission were cardiac conditions (53%), mainly ACS, which accounted for 42.6% of the total. The high prevalence of cardiac causes of readmission was also reported by Khawaja et al.⁹ (69%) evaluating 30-day readmission rates after percutaneous coronary intervention. Belitardo and Ayoub¹ also found a higher frequency of ACS (41.6%) among readmissions.

First hospitalization and readmission may occur for the same diagnosis due to the lack of resolution of the primary cause, which characterizes an avoidable readmission.¹ Avoidable readmissions are considered those that are the result of a situation that if managed differently might have prevented the admission.³²

These findings were similar to those reported by Ricci et al.⁸ showing a higher prevalence of cardiac causes of readmissions. Besides, increased risk of readmissions due to cardiac causes after the first ACS event has been reported.⁷ In the study by Kwok et al.,³³ although noncardiac causes were present in half of readmissions, cardiac causes were responsible for 46% of the cases, with chest pain of noncardiac origin and ACS the most prevalent diagnoses, respectively.

Different risk predictors of hospital readmission have been described in the literature. This may be explained by different characteristics of the study populations, including the presence of comorbidities, and particularities of health care centers.

Hospital readmissions may be related to several factors, such as patient's clinical condition, family and social support, and the quality of health care received during and after hospitalization. The high readmission rates draw attention to the need for the development of actions during hospitalization, at discharge, and during follow-up, considering patients' individual features, in order to reduce the number of readmissions.^{20,34}

Our study has some limitations that should be considered. The lack of detailed information about the medications used by the patients and possible losses to follow-up. The readmissions were evaluated in the four main and referral cardiology hospitals of the city and therefore, a higher number of readmissions was somehow expected; we did not evaluate the occurrence of readmission in other hospitals in the city or in other cities. In addition, among these four institutions, there was only one public hospital, which requires referral for admission. These factors may have led to an underestimation of readmissions. On the other hand, this study design can be used to measure predictor variables before the occurrence of readmissions.

Conclusion

ACS was the main cause of readmissions within one year after the first admission, with higher prevalence among users of supplemental health care. The main determinants of readmission were the type of health care provided, and a previous diagnosis of congestive heart failure. The present study adds to the knowledge on determinants of readmission and may serve as a basis for implementation of assistance strategies that may reduce the occurrence of new admissions in medium- and long term, leading to better prognosis and lower costs to the health system.

Author contributions

Conception and design of the research: Oliveira LMSM, Costa IMNBC, Silva DG, Silva JRS, Buarque MDBM, Sousa ACS; Acquisition of data: Oliveira LMSM, Costa IMNBC, Buarque MDBM, Sousa ACS; Analysis and interpretation of

the data: Oliveira LMSM, Costa IMNBC, Silva DG, Silva JRS, Barreto Filho JAS, Almeida-Santos MA, Oliveira JLM, Vieira DAS, Sousa ACS; Statistical analysis: Silva DG, Silva JRS, Vieira DAS; Writing of the manuscript: Oliveira LMSM, Costa IMNBC, Silva DG, Barreto Filho JAS, Almeida-Santos MA, Oliveira JLM, Vieira DAS, Sousa ACS; Critical revision of the manuscript for intellectual content: Oliveira LMSM, Silva DG, Barreto Filho JAS, Almeida-Santos MA, Oliveira JLM, Vieira DAS, Sousa ACS.

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 Larissa Marina Santana, from Universidade Federal de Sergipe.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Sergipe under the protocol number 2.203.855 / 302.544. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Belitardo JN, Ayoub AC. Identification of readmission predictors in elderly patients with acute coronary syndrome. *Int J Cardiovasc Sci*. 2015;28(2):139-47.
2. Louvison MC, Lebrão ML, Duarte YA, Santos JL, Malik AM, Almeida ES. Desigualdades no uso e acesso aos serviços de saúde entre idosos do município de São Paulo. *Rev Saúde Pública*. 2008;42(4):733-40.
3. McManus DD, Nguyen HL, Saczynski JS, Tisminetzky M, Bourell P, Goldberg RJ. Multiple cardiovascular comorbidities and acute myocardial infarction: Temporal trends (1990-2007) and impact on death rates at 30 days and 1 year. *Clin Epidemiol*. 2012;4(1):115-23.
4. Costa IM, Silva DG, Barreto-Filho JA, Oliveira JL, Silva JR, Buarque MD, et al. Diet quality of patients with acute coronary syndrome receiving public and private health care. *Nutrition*. 2019 Mar;59:131-7.
5. Panagiotakos DB, Notara V, Georgousopoulou EN, Pitsavos C, Antonoulas A, Kogias Y, et al. A comparative analysis of predictors for 1-year recurrent acute coronary syndromes events, by age group: The Greek observational study of ACS (GREECS). *Maturitas*. 2015;80(2):205-11.
6. Steca P, Monzani D, Greco A, Franzelli C, Magrin ME, Miglioretti M, et al. Stability and change of lifestyle profiles in cardiovascular patients after their first acute coronary event. *PLoS One*. 2017;12(8):e0183905.
7. Southern DA, Ngo J, Martin BJ, Galbraith PD, Knudtson ML, Ghali WA, et al. Characterizing types of readmission after acute coronary syndrome hospitalization: implications for quality reporting. *J Am Heart Assoc*. 2014;3(5):e001046.
8. Ricci H, De Araújo MN, Simonetti SH. Readmissão precoce em hospital público de alta complexidade em cardiologia. *Rev Rene*. 2016;17(6):828-34.
9. Khawaja FJ, Shah ND, Lennon RJ, Lusser JP, Alkatib AA, Rihal CS, et al. Factors associated with 30-day readmission rates after percutaneous coronary intervention. *Arch Intern Med*. 2012;172(2):112-7.
10. World Health Organization (WHO). Diet, nutrition and the prevention of chronic diseases. Geneva;1990. (Report of a WHO group. Technical Report Series. No 797).
11. Lebrão ML, Duarte YAO (orgs). SABE - Saúde, Bem-estar e Envelhecimento - O Projeto Sabe no município de São Paulo: uma abordagem inicial. Brasília: Organização Pan-Americana da Saúde (OPAS); 2003.
12. Matsudo S, Araújo T, Matsudo V, Andrade D, Andrade E, Oliveira L, et al. Questionário Internacional de Atividade Física (IPAQ): estudo de validade e reprodutibilidade no Brasil. *Rev Bras de Ativ Fís Saúde*. 2001;6(2):5-12.
13. IPAQ Research Committee. Guidelines for the data processing and analysis of the International Physical Activity Questionnaire. No. 2005. [Cited in 2018 Jun 12]. Available from: <http://www.ipaq.ki.se/scoring.pdf>.
14. R Core Team (2016) R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. Vienna, Austria.
15. Dreyer RP, Dharmarajan K, Kennedy KF, Jones PG, Vaccarino V, Murugiah K, et al. Sex Differences in 1-Year All-Cause rehospitalization in patients after acute myocardial infarction. *Circulation*. 2017;135(6):521-53.

16. Sangu PV, Ranasinghe I, Aliprandi Costa BA, Devlin G, Elliot J, Lefkowitz, et al. Trends and predictors of rehospitalisation following an acute coronary syndrome: report from the Australian and New Zealand population of the Global Registry of Acute Coronary Events (GRACE). *Heart*. 2012;98(23):1728-31.
17. Gheorghide M, Vaduganathan M, Fonarow GC, Bonow RO. Rehospitalization for Heart Failure. *J Am Coll Cardiol*. 2013;61 (4):391-403.
18. Reis MB, Dias MG, Bibanco MS, Lopes CT, Gea NG. Readmissão hospitalar por insuficiência cardíaca em um hospital de ensino. *Medicina (Ribeirão Preto)*. 2015;48(2):138-42.
19. Mendes EV. As redes de atenção à saúde. *Cien Saude Colet*. 2010;15(5):2297-305.
20. Sousa FOS, De Medeiros KR, Gurgel Júnior GD, De Albuquerque PC. Do normativo à realidade do Sistema Único de Saúde: revelando barreiras de acesso na rede de cuidados assistenciais. *Cien Saude Colet*. 2014; 19(4):1283-93.
21. Fischer C, Steyerberg EW, Fonarow GC, Ganiats TG, Lingsma HF. A systematic review and meta-analysis on the association between quality of hospital care and readmission rates in patients with heart failure. *Am Heart J*. 2015;170(5): 1005-17.
22. Ziaeiiana B, Fonarow GC. The prevention of hospital readmissions in heart failure. *Prog Cardiovasc Dis*. 2016;58(4):379-85.
23. Barreiros BRN, Bianchi ERF, Turrini RNT, Poveda VB. Causas de readmissão hospitalar após cirurgia cardíaca. *Rev Eletr Enf*. 2016;18:e1182
24. Mirkin KA, Enomoto LM, Caputo GM, Hollenbeak CS. Risk factors for 30-day readmission in patients with congestive heart failure. *Heart Lung*. 2017;46(5):357-62.
25. Van Walraven C, Jennings A, Forster AJ. A meta-analysis of hospital 30-day avoidable readmission rates. *J Eval Clin Pract*. 2012;18(6):1211-8.
26. Bradley EH, Curry L, Horwitz LI, Sipsma H, Wang Y, Walsh MN, et al. Hospital strategies associated with 30-day readmission rates for patients with heart failure. *Circ Cardiovasc Qual Outcomes*. 2013;6(4):444-50.
27. Malta DC, Stopa SR, Pereira CA, Szwarcwald CL, Oliveira M, Reis AC. Cobertura de planos de saúde na população brasileira, segundo a Pesquisa Nacional de Saúde, 2013. *Cien Saude Colet*. 2017;22(1):179-90.
28. Malta DC, Bernal RTI. Comparação dos fatores de risco e proteção de doenças crônicas na população com e sem planos de saúde nas capitais brasileiras, 2011. *Rev Bras Epidemiol*. 2014;17(1):241-55.
29. Instituto Brasileiro De Geografia e Estatística (IBGE). Pesquisa de orçamentos familiares 2008-2009. Perfil das despesas no Brasil - indicadores selecionados. Brasília;2012.
30. Sociedade Brasileira de Cardiologia. IV Guidelines of Sociedade Brasileira de Cardiologia for treatment of acute myocardial infarction with STsegment elevation. *Arq Bras Cardiol*. 2009;93(6 Suppl 2):e179-264. Erratum in: *Arq Bras Cardiol*. 2010;95(4):553.
31. Sociedade Brasileira de Cardiologia. Diretriz de telecardiologia no cuidado de pacientes com síndrome coronariana aguda e outras doenças cardíacas. *Arq Bras Cardiol*. 2015;104(5 Suppl 1):1-26.
32. Redfern J, Hyun K, Santo K. Challenges and opportunities associated with quantification of cardiovascular readmissions. *J Am Heart Assoc*. 2014;3(5):1-3.
33. Kwok HS, Wong CW, Shufflebotham H, Brindley L, Fatima T, Shufflebotham A, et al. Early readmissions after acute myocardial infarction. *Am J Cardiol*. 2017;120(5):723-8.
34. Barekatain M, Maracy MR, Hassannejad R, Hosseini R. Factors associated with readmission of patients at a university hospital psychiatric Ward in Iran. *Psychiatry J*. 2013;2013:685625.



Hospital Readmissions after Acute Coronary Syndromes

Alfredo J. Mansur 

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

Short Editorial related to the article: Readmission of Patients with Acute Coronary Syndrome and Determinants

Acute ischemic syndromes (myocardial infarction, unstable angina) may occur *de novo* in previously asymptomatic patients or may occur in the course of chronic diseases. After hospital-based acute care therapy, with or without percutaneous or surgical intervention, patients are discharged and receive advice for long-term therapy. However, some patients develop symptoms again in the short-term course and are readmitted to the hospital due to clinical as well as non-clinical causes and with clinical and other non-clinical consequences.¹

Hospital readmissions deserve studies in different settings and have been reported in medical literature. In one report, the readmission rate after one year in patients older than 65 years surviving myocardial infarction was 49.9% in 4,767 hospitals in United States of America between 2008 and 2010; the readmission rate, as well as mortality, were higher in the first months after discharge and decreased thereafter over 12 months.² Additional studies compared not-for-profit hospitals (15.7%) with proprietary hospitals (16.6%) regarding readmission rates in the first month of discharge without demonstrating an association of hospital ownership with the success in programs devoted to decrease readmission rate; the results of such interventions were not statistically different between the two types of hospitals.³ Socioeconomic and ethnic factors were systemic influences

without overt manifestations in a specific hospital.⁴ In many instances, the readmission rate was studied as a surrogate marker of quality of care;⁵⁻⁷ the heterogeneity of patients and medical conditions made a clear association with the index admission elusive and not easily predicted.⁵

In this issue, colleagues from Aracaju (Sergipe, Brazil) report the study⁸ of a hospital-based sample of 536 eligible patients with acute coronary syndrome admitted to three private hospitals (where costs are usually paid by the patient or through an insurance group) and one public hospital (supported by the government, either city, state or federal government) to scrutinize variables associated with re-admissions. They observed the readmission rate was high (115/536, 21.4%) and the mortality of the readmitted patients was also high - 7%. Acute coronary syndromes and heart failure were the leading causes of hospital readmission, mainly in patients admitted to private hospital facilities,⁸ probably related to characteristics of the access. The authors recognize that a hospital-based study sample without full follow-up data are limitations that may stimulate following the previous suggestion to remain vigilant² for health deterioration after discharge from in-hospital treatment, emphasizing the importance of continuous medical advice, support, and therapy. A previous study with a small sample (Maceió, AL) in the same region of the city of the current study suggested low adherence of patients to medical therapy as a significant influence on the frequency of readmissions and mortality.⁹

Finally, further studies and interventions are to be stimulated in other cities and different clinical settings, either hospital-based or at community medical facilities, taking into consideration local challenges and opportunities to make therapy more successful by preventing clinical deterioration that need hospital re-admissions after a period of in-hospital treatment of acute ischemic syndromes.

Keywords

Acute Coronary Syndrome; Myocardial Infarction; Hospitalization; Patient Readmission; Hospitals Private; Mortality.

Mailing Address: Alfredo J. Mansur •

Av. Dr. Eneas de Carvalho Aguiar, 44, Cerqueira César. Postal Code 05403-900, São Paulo, SP – Brazil

E-mail: alfredo.mansur@incor.usp.br

DOI: 10.5935/abc.20190136

References

1. Fingar K (Truven Health Analytics), Washington R (AHRQ). Trends in Hospital Readmissions for Four High-Volume Conditions, 2009–2013. HCUP Statistical Brief #196. November 2015. Agency for Healthcare Research and Quality, Rockville, MD. [Cited in 2019 June 25]. Available from: <http://www.hcup-us.ahrq.gov/reports/statbriefs/sb196-Readmissions-Trends-High-Volume-Conditions.pdf>.
2. Dharmarajan K, Hsieh AF, Kulkarni VT, Lin Z, Ross JS, Horwitz LJ, et al. Trajectories of risk after hospitalization for heart failure, acute myocardial infarction, or pneumonia: retrospective cohort study. *BMJ*. 2015 Feb 5;350:h411.
3. Birmingham LE, Oglesby WH. Readmission rates in not-for-profit vs. proprietary hospitals before and after the hospital readmission reduction program implementation. *BMC Health Serv Res*. 2018;18(1):31.
4. Downing NS, Wang C, Gupta A, Wang Y, Nuti SV, Ross JS, et al. Association of Racial and Socioeconomic Disparities With Outcomes Among Patients Hospitalized With Acute Myocardial Infarction, Heart Failure, and Pneumonia: An Analysis of Within- and Between-Hospital Variation. *JAMA Netw Open*. 2018;1(5):e182044.
5. Southern DA, Ngo J, Martin BJ, Galbraith PD, Knudtson ML, Ghali WA, et al. Characterizing types of readmission after acute coronary syndrome hospitalization: implications for quality reporting. *J Am Heart Assoc*. 2014;3(5):e001046.
6. Strom JB, Yeh RW. Should We Care About Short-Term Readmissions After Percutaneous Coronary Intervention? *Circ Cardiovasc Interv*. 2017;10(12). pii: e006123.
7. Arnold SV, Smolderen KG, Kennedy KF, Li Y, Shore S, Stolker JM, et al. Risk factors for rehospitalization for acute coronary syndromes and unplanned revascularization following acute myocardial infarction. *J Am Heart Assoc*. 2015;4(2). pii: e001352.
8. Oliveira LMSM, Costa IMNBC, Silva DG, Barreto-Filho JAS, Santos MAA, Oliveira JLM, et al. Readmission of Patients with Acute Coronary Syndrome and Determinants. *Arq Bras Cardiol*. 2019; 113(1):42-49.
9. Oliveira-Filho AD, Morisky DE, Costa FA, Pacheco ST, Neves SF, Lyra DP Jr. Improving post-discharge medication adherence in patients with CVD: a pilot randomized trial. *Arq Bras Cardiol*. 2014;103(6):503-12.



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

Association of Dietary Patterns with Excess Weight and Body Adiposity in Brazilian Children: The Pase-Brasil Study

Naruna Pereira Rocha,^{1D} Luana Cupertino Milagres,^{1D} Mariana De Santis Filgueiras,^{1D} Lara Gomes Suhett,^{1D} Mariane Alves Silva,^{1D} Fernanda Martins de Albuquerque,^{1D} Andréia Queiroz Ribeiro,^{1D} Sarah Aparecida Vieira,^{1D} Juliana Farias de Novaes^{1D}

Departamento de Nutrição e Saúde - Universidade Federal de Viçosa, Viçosa, MG – Brazil

Abstract

Background: Obesity is a multifactorial disease and a serious public health problem. Some of the associated factors are modifiable and, among them, the diet is highlighted.

Objective: To evaluate the association of dietary patterns of schoolchildren with obesity and body adiposity.

Methods: A cross-sectional study was carried out with 378 children aged 8 and 9 years, enrolled in urban schools in the city of Viçosa, Minas Gerais, Brazil. A semi-structured questionnaire was applied to the children and their caregivers on sociodemographic characteristics and life habits. Three 24-hour food recalls were used to identify dietary patterns; the Principal Component Analysis was employed. Weight and height were measured for the calculation of the body mass index (BMI) of the children and their mothers, waist circumference and neck circumference. Body composition was also evaluated through dual-energy X-ray absorptiometry (DXA). For all performed tests, the level of significance was set at 5%.

Results: Five dietary patterns (DP) were identified: “unhealthy”, “snacks”, “traditional”, “industrialized” and “healthy”. There was an association between excess weight (prevalence ratio [PR]: 1.38, 95% confidence interval [95%CI]: 1.02 to 1.87) and body fat (PR: 1.32, 95%CI : 1.07 to 1.64) with industrialized DP. There was an association between excess body fat (PR: 1.31, 95%CI: 1.01 to 1.74) and lower adherence to traditional DP. The other patterns were not associated with obesity and body adiposity.

Conclusion: Children with excess weight and body adiposity showed greater adherence to the industrialized DP and lower adherence to the traditional DP. We suggest that early assessments of dietary habits should be undertaken for monitoring and modifying these habits when necessary. (Arq Bras Cardiol. 2019; 113(1):52-59)

Keywords: Child; Obesity; Adiposity; Hyperphagia; Feeding Behavior; Factor Analysis, Statistical; Epidemiology

Introduction

Childhood obesity is considered a serious public health problem.¹ According to the World Health Organization (WHO, 2016),² approximately 41 million children worldwide under five years of age have excess weight or obesity. In Brazil, the prevalence of obesity is increasing, and data related to childhood excess weight show that it is increasing in children from five to nine years of age more rapidly than in other age groups.³

Obesity can be considered a multifactorial disease due to genetic predisposition, sedentary lifestyle, availability of food inside and outside the home environment, inadequate and structural food patterns, such as food production and distribution systems, all of which play important roles in the etiology of this alteration.^{4,5}

Among the several risk factors for obesity, the diet constitutes a modifiable factor and has been related to the onset of chronic diseases and cardiometabolic alterations.^{6,7} Several studies have shown that energetically dense, fiber-poor and refined carbohydrate-rich diets are associated with obesity in adults.^{8,9} In children, most of the results are based on the analysis of isolated foods or nutrients, and studies on dietary patterns are scarce.^{10,11}

The analysis of dietary patterns allows the evaluation of the diet from a global perspective, favoring the implementation of strategies to promote healthy eating habits and prevention of nutrient-related diseases and conditions.¹² As childhood is a period of formation of eating habits,¹³ initiatives that allow identifying inappropriate dietary practices and associating them with excess body weight and adiposity could help to prevent chronic diseases, as well as to reduce short and long-term health damage by encouraging and adopting healthy habits.¹⁴

Considering the above, the aim of this study was to evaluate the association of eating patterns of schoolchildren with obesity and body adiposity. Our hypothesis is that unhealthy eating patterns are associated with excess weight and body adiposity in Brazilian children.

Mailing Address: Naruna Rocha •

Rua Doutor Milton Bandeira, 240. Postal Code 36570-172, Centro, Viçosa, MG – Brazil

E-mail: narunarocho@hotmail.com, narunarocho@gmail.com

Manuscript received February 27, 2018, revised manuscript April 04, 2018, accepted November 14, 2018

DOI: 10.5935/abc.20190113

Methods

Study population and design

This is a cross-sectional study, with a representative sample of 378 children from public and private schools in the urban area of the municipality of Viçosa, state of Minas Gerais, Brazil. The participants of this study came from the Schoolchildren Health Assessment Survey (PASE, *Pesquisa de Avaliação da Saúde do Escolar*). The PASE aimed to investigate the cardiovascular health of children in the city of Viçosa, MG.

The municipality of Viçosa is located in Zona da Mata Mineira, 227 km from the capital city, Belo Horizonte. Viçosa has a land area of 299 km² and 72,244 inhabitants, with 67.3% residing in the urban area.¹⁵

In 2015, the municipality had 17 public schools and 7 private ones, which were attended by 8- and 9-year-old children in the urban area, totaling a population of 1,464 children enrolled in these schools. The sample was calculated using the OpenEpi statistical program (Version 3.01), considering a prevalence of 11.8% for obesity in the age group,¹⁶ a tolerable error of 5%, plus 10% of losses and 10% of confounding factors, totalizing a sample size of 392 children. The final sample included 378 children, with a sample loss of 3.6%. The losses were due to non-compliance with all stages of the study.

The sampling process was carried out in two stages. First, stratified casual sampling was performed, in which the number of children to be sampled from each school was proportional to the total number of students in each school. Subsequently, the lots were drawn by using a random number table, to complete the required number of students from the 24 public and private schools in the urban area that were attended by the assessed age group.

The non-inclusion criteria for this study were the lack of contact with the parents or guardians after three attempts to contact them, children with some clinical or nutritional alterations that could interfere with food consumption, nutritional status and body composition, as well as children with physical, cognitive or multiple disabilities.

This study was carried out in accordance with the guidelines established in the Declaration of Helsinki and was initiated only after approval by the Ethical Committee for Research in Human Beings of Universidade Federal de Viçosa (UFV) (Opinion n. 663.171/2014). The study was also approved by the Municipal Education Secretariat, Regional Superintendence of Education and the school principals. All parents and children were informed about the purpose of the study, and all the children's parents/guardians signed the Free and Informed Consent form.

Food consumption

Food consumption assessment was performed by applying three 24-hour food recalls (R24h) on non-consecutive days, including one weekend day and a 15-day mean interval between them, based on information provided by the mother/guardian and by the child. For the children who consumed part of the food in the school environment, the

researchers obtained the information from the schools, such as recipes and portions of the foods offered, in addition to confirming with the children what had been consumed. For those children who used to bring their food from home, the parents/guardians were asked about food and beverages offered and their amounts. The three food recalls were applied by trained nutritionists.

The food consumption data obtained through the three R24h were tabulated and processed in Dietpro® 5i software, version 5.8.¹⁷

Anthropometric data

All anthropometric measurements were performed by a trained nutritionist, selected after calibration of the team members. Weight was measured using a digital electronic scale, with a capacity of 150 kg and sensitivity of 50 g (Tanita®, model BC 553, Arlington Heights, IL, USA). Height was measured using a vertical stadiometer, divided in centimeters and subdivided in millimeters (Alturaexata®, Belo Horizonte, MG, Brazil).

The nutritional status was assessed by body mass index (BMI), with BMI cutoff points by age calculated in z-scores according to the World Health Organization (WHO) parameters (2007)¹⁸ as thinness, normal weight, overweight and obesity. Excess weight was considered for the overweight and obesity categories.

The waist circumference was obtained by measuring the midpoint between the iliac crest and the last rib using an inelastic measuring tape, divided in centimeters and subdivided in millimeters. Abdominal obesity was considered when the waist circumference was equal to the 90th percentile of the sample itself, following the guidelines of the International Diabetes Federation (2007).¹⁹

The waist-to-height ratio (WHtR) was obtained by the waist circumference measurement divided by height. The cutoff point ≥ 0.5 was used as the risk for the development of cardiovascular diseases.²⁰

The neck circumference (NC) was measured at the level of the thyroid cartilage using an inelastic measuring tape, divided in centimeters and subdivided in millimeters. The cutoff points proposed by Nafiu et al. (2010)²¹ for the detection of excess body fat in children were used for NC classification.

The children's body composition was assessed through DXA by a specialized technician, obtaining the fat mass measurement. The children were evaluated in the morning, in fasting condition, in the supine position. Body fat was classified using the cutoff points proposed by Lohman (1992),²² and the cutoff points for overweight risk and overweight were considered as excess body fat.

Adjustment variables

Potential adjustment variables were selected according to the previous literature.²³⁻²⁵ The collection of these variables was performed by nutritionists, using a questionnaire created by the researchers themselves. The questionnaire was previously tested in a pilot study, and the sample consisted of children aged 8 and 9 years.

The assessed sociodemographic variables were gender and self-reported ethnicity of the child, maternal schooling, family and *per capita* income, and the type of school in which the child was enrolled (public or private).

The behavioral variables were omission of breakfast and sedentary behavior. All questions were answered by parents or guardians. Breakfast consumption was assessed by the first food intake that the child consumed and/or drank within the first 2 hours after waking up.²⁴

Sedentary behavior was assessed as time spent by the child in activities that did not increase energy expenditure, such as watching television or engaging in other forms of screen-based entertainment. The used cutoff point was screen time ≥ 2 hours/day, according to the American Academy of Pediatrics (2013).²⁵

Maternal weight and height were measured using an electronic digital scale, with a capacity of 150 kg and sensitivity of 50 g (Tanita®, model BC 553, Arlington Heights, IL, USA) and a vertical stadiometer, divided in centimeters and subdivided in millimeters (Alturaexata®, Belo Horizonte, MG, Brazil), respectively. Using these data, it was possible to calculate the BMI and to classify it according to the WHO parameters (1998).²⁶

Statistical analysis

Descriptive statistics were used to characterize the sample according to sociodemographic, behavioral characteristics, nutritional status and body composition. At this phase, each variable was assessed through the distribution of absolute and relative frequencies.

The normality of the variables was evaluated by the Shapiro-Wilk test, in addition to the evaluation of graphical methods (histogram), kurtosis and asymmetry verification to classify variables regarding normality.

Aiming to identify the food pattern, the foods covered by the R24h were measured in grams/day (g/d) or milliliters/day (mL/d) and collected as isolated foods or food groups by nutritional similarity and their contribution to the hypothesis of diet-disease associations. Moreover, foods consumed by less than 10% of the assessed population were excluded or grouped.²⁷ To identify the patterns, all foods in milliliters/day were transformed into grams/day according to the density table of the Food and Agriculture Organization (FAO, 2012).²⁸

Pattern identification was carried out using an *a posteriori* methodology, through the Principal Component Analysis (PCA). Before starting the analysis, the sample size was carefully evaluated in relation to the food groups formed in the PCA analyses.²⁹

For the PCA analysis, the results of the Kaiser-Meyer-Olkin test (KMO = 0.58) and the Bartlett sphericity test ($p < 0.001$) were estimated. They evaluate whether the data can be used in the PCA.²⁹ The varimax rotation was performed to facilitate the interpretation of the obtained results, in which factorial loads ≥ 0.25 (positive or negative) were retained.²⁴ The number of extracted factors was defined according to the

eigenvalue criterion > 1 followed by the scree plot graph of variance by the number of components, in which the points on the maximum slope indicated the number of components to be retained. The nomenclature of the found patterns was attributed according to the characteristics of the foods/formed groups and extracted by PCA.

Dietary patterns were presented as explanatory variables, and the schoolchildren's dietary patterns scores were categorized according to the 75th percentile of the sample.

The Mann-Whitney test was performed to compare the medians of the anthropometric variables and body composition according to the classification of the dietary patterns.

The crude analysis was performed using Poisson regression models with robust variance, having anthropometry and body composition as dependent variables. The variables considered important in the assessed association were used for the model adjustment, such as gender, maternal BMI, total energy consumption (kcal) and breakfast consumption.

The prevalence ratio (PR) with 95% confidence interval (95% CI) was used as a measure of association. For all performed tests, the level of significance was set at 5%. Statistical analyses were performed using the Stata program version 13.0.

Results

It was observed that more than half of the children had a sedentary behavior (74.9%) and mothers with excess weight (56.9%). Breakfast omission was observed in almost 20.0% of the sample (Table 1).

The PCA analysis identified five dietary patterns (DP): (i) unhealthy DP, consisting of foods/groups of simple sugars and chocolate, fat-rich snacks and whole dairy foods; (ii) snacks DP, consisting of bakery products/food groups and infusions; (iii) traditional DP, consisting of rice, beans, flours, tubers and cereals; (iv) industrialized DP, consisting mainly of ultra-processed products; (v) healthy DP, consisting of foods rich in complex carbohydrates and high biological value proteins (Table 2).

Higher median BMI values ($p = 0.001$), body fat percentage ($p = 0.002$), waist circumference ($p = 0.004$), waist-to-height ratio ($p = 0.030$) and neck circumference ($p = 0.001$) were observed in children with higher consumption of the industrialized DP (Table 3).

In the crude analysis of the regression model, a higher prevalence of increased neck circumference was found in children with higher consumption of snacks DP (PR: 1.79; 95% CI: 1.13 to 2.85). Children with excess weight (PR: 1.58; 95% CI: 1.18 to 2.10) and body fat (PR: 1.50; 95% CI: 1.23 to 1.82) showed higher adherence to the industrialized DP (Table 4).

After the adjusted regression analysis, it was observed that children with excess weight (PR: 1.38, 95%CI: 1.02 to 1.87) and body fat (PR: 1.32, 95%CI: 1.07 to 1.64) showed greater adherence to the industrialized DP. Additionally, children with excess body fat (PR: 1.31; 95%CI: 1.01 to 1.74) showed lower adherence to the traditional DP (Figure 1).

Table 1 – Sample characterization according to socioeconomic, behavioral variables and maternal nutritional status of the children. Viçosa, MG, Brazil, 2015

Variable	N	%
Age		
8 years	183	48.4
9 years	195	51.6
Gender		
Female	197	52.1
Male	181	47.9
Child Ethnicity /skin color		
White	119	31.5
Non-white	259	68.5
Type of School		
Public	268	70.9
Private	110	29.1
Maternal schooling		
> 9 years	234	62.2
= 9 years	142	37.8
per capita income tertiles		
= 1500.0	133	35.2
> 1599.0 to 2340.98	117	31.0
> 2340.98	128	33.8
Screen time		
< 2 hours/day	95	25.1
= 2 hours/day	283	74.9
Maternal excess weight		
No	127	43.1
Yes	168	56.9
Breakfast omission		
No	303	80.2
Yes	75	19.8

Discussion

In the present study, five dietary patterns were identified: unhealthy, snacks, traditional, industrialized and healthy. Children with excess weight and body adiposity showed greater adherence to the industrialized DP. Moreover, children with lower adherence to the traditional DP had higher adiposity prevalence.

The comparison of dietary patterns from different studies is difficult to make due to cultural, geographical and methodological differences.⁵ However, despite the complexity, the dietary patterns identified in this study are similar to those found in other national and international studies.^{30,31} Among Brazilian children aged 8 and 9 years, Villa et al. (2015)³¹ identified five food patterns: traditional pattern, consisting of rice, beans, roots and tubers and beef; DP of sweetened beverages and snacks, characterized by

ultra-processed foods with high fat content and refined sugars; monotonous pattern, consisting of whole milk and chocolate; healthy pattern, characterized by the consumption of fibers and white meats; and the ovo-lacto pattern, characterized by the consumption of eggs, cheeses and sweetened milk-based beverages. Ambrosini et al. (2012)¹⁰ identified an energetically dense, high-fat, low-fiber DP in children and adolescents from 7 to 13 years of age. Durão et al. (2017)³⁰ identified three patterns at 4 years of age, named energetically dense, snacks and healthy. Overall, industrialized DPs, rich in fats and refined carbohydrates, predominate in this population.

It is worth noting that the unhealthy pattern includes the participation of whole dairy products, foods that are recommended in childhood to guarantee the adequate supply of calcium and high biological value protein, essential for adequate growth in childhood.³² However, in the assessed population, milk consumption is attained with the addition of chocolate-flavored powder and simple sugars. This habit is common in childhood, but may lead to the consumption of a hypercaloric diet, predisposing to the risk of obesity and cardiometabolic alterations.^{32,33}

The industrialized DP identified in this study consists of processed and ultra-processed foods, rich in simple sugars and fats, nutrients that favor lipogenesis, excess weight and an increase in metabolic complications in childhood.^{10,34} In this study, the prevalence of excess of body weight and adiposity were higher in the children with higher consumption of the industrialized DP. Studies have reported that low fruit and vegetable intake, associated with increased intake of fats and processed foods may increase the risk of obesity.^{6,30} A possible explanation for this association is that the usual consumption of a high-fat diet tends to impair appetite control, leading to hyperphagia due to the greater palatability of fatty foods, resulting in higher energy consumption.³⁵ The higher consumption of fat, simple sugars and sweetened beverages by individuals with excess weight may also be explained by their lower effect on satiety when compared to other macronutrients.³⁵

Children with excess body fat showed lower adherence to the traditional DP. The traditional pattern identified in this study is characterized by the consumption of rice and beans, as well as other carbohydrates. Beans are a legume source of soluble and insoluble proteins, minerals, vitamins, and soluble and insoluble fibers, which, when routinely consumed, may be associated with a reduced risk of cardiovascular diseases.³⁶ Kupek et al. (2016),³⁷ when evaluating dietary patterns in schoolchildren aged 7 to 10 years, concluded that children who consumed rice and beans had a lower risk of obesity.

Some studies evaluating the association between dietary patterns and body composition in children found similar results to ours. Durão et al. (2017)³⁰ observed that girls with the highest adherence to the high-energy density diet, consisting mainly of sweets, soft drinks, pastries and processed meats, had higher values of BMI, WHtR and body fat. Zhang et al. (2015),³⁸ assessing Chinese children and adolescents, found that the modern dietary pattern of northern China was associated with an increased risk of obesity. Shang et al. (2012)⁷ observed that obesity was more prevalent in children who adopted the western dietary pattern, when compared to those who consumed the traditional healthy pattern.

Table 2 – Distribution of factorial loads for the five identified food patterns. Viçosa, MG, Brazil, 2015

Foods	Dietary Patterns				
	Unhealthy	Snacks	Traditional	Industrialized	Healthy
Breads, biscuits and cakes without frosting		0.797			
Milk and dairy products	0.663				
Rice	-0.432		0.592		
Beans			0.61		
Sugar and chocolate milk	0.765				
Infusions	-0.555	0.361			
Butter and margarine		0.632			
Fruits and natural fruit juice				-0.519	0.295
Pasta			-0.258	0.276	
Flours, tubers and cereals			0.629		
Meat and eggs					0.507
Fat-rich snacks and sauces	0.428				
Vegetables				-0.307	0.679
Green vegetables					0.693
Sweets, candy		-0.256		0.448	
Artificial beverages				0.763	
Number of Items	5	4	4	5	4
Eigenvalues	2.30	1.72	1.50	1.25	1.10
% Explained variance	11.53	9.99	9.97	9.02	8.79
Total explained variance					
Kaiser-Meyer-Olkin (KMO) = 0,58 por:	49.33				
Kaiser-Meyer-Olkin (KMO) = 0.58					

Table 3 – Median (IQ) of the anthropometric variables and body composition, according to the consumption percentiles of children's dietary patterns. Viçosa, MG, Brazil, 2015

	Unhealthy DP		Snacks DP		Traditional DP		Industrialized DP		Healthy DP	
	<p75	≥p75	<p75	≥p75	<p75	≥p75	<p75	≥p75	<p75	≥p75
BMI	16.5 (15.0-19.3)	16.53 (15.09-19.57)	16.49 (15.0-19.4)	16.75 (15.1-19.1)	16.65 (14.9-19.3)	16.25 (15.3-19.8)	16.22 (14.9-18.7)	17.94 (15.8-21.0)*	16.49 (14.9-19.6)	16.78 (15.3-19.1)
%BF	17.6 (10.8-29.3)	18.2 (11.6-27.0)	19.1 (11.1-29.3)	16.7 (10.9-27.4)	18.7 (10.6-29.0)	17 (11.6-30.0)	16.7 (10.6-26.1)	22.5 (12.0-32.2)*	17.7 (10.6-29.2)	19.7 (12.5-29.0)
WC	59.6 (54.8-68.8)	60.0 (55.6-68.2)	59.0 (55.0-68.5)	60.5 (55.0-68.8)	59.0 (54.4-68.1)	59.0 (55.5-69.1)	58.0 (54.5-66.0)	62.0 (56.5-72.0)*	58.8 (54.7-68.1)	59.7 (55.6-68.8)
WHtR	0.19 (0.1-0.2)	0.19 (0.1-0.2)	0.19 (0.1-0.2)	0.18 (0.16-0.21)	0.19 (0.2-0.2)	0.19 (0.15-0.21)	0.18 (0.1-0.2)	0.20 (0.1-0.3)*	0.19 (0.1-0.2)	0.19 (0.1-0.2)
NC	26.9 (25.9-28.3)	27.3 (26.3-28.6)	26.9 (26.0-28.3)	27.2 (26.0-28.8)	26.9 (25.9-28.3)	27.4 (26.0-28.5)	26.8 (25.7-28.1)	27.7 (26.5-29.0)*	27 (25.9-28.5)	27.3 (26.0-28.5)

DP: Dietary Pattern; IQ: interquartile range for the 25th and 75th percentiles; BMI: body mass index; %BF: percentage of body fat; WC: waist circumference; WHtR: waist-to-height ratio; NC: neck circumference. Mann-Whitney test. * Statistical significance ($p < 0.05$)

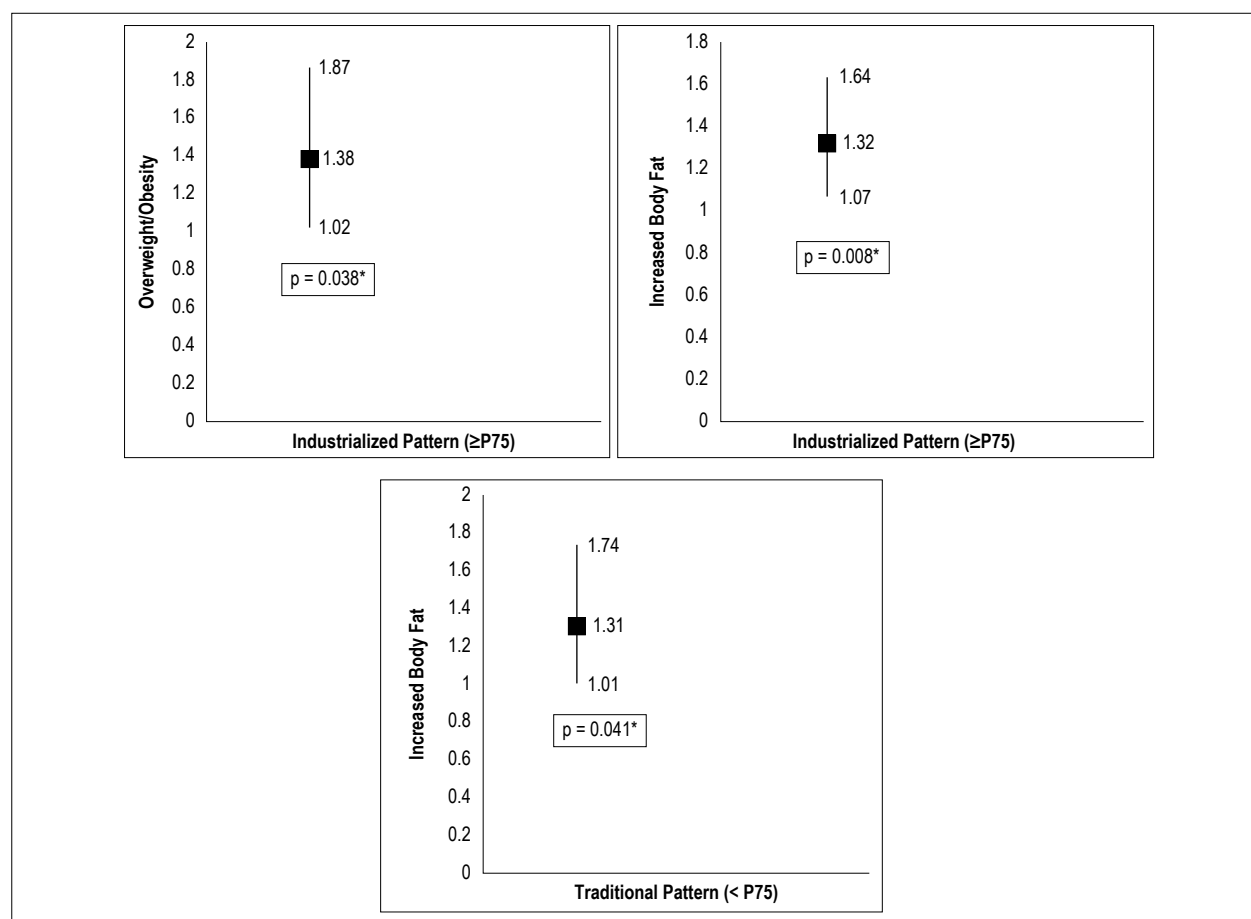


Figure 1 – Association between dietary patterns and adiposity in children. Viçosa, MG, Brazil, 2015.

Table 4 – Unadjusted association between adiposity measures and dietary patterns in children. Viçosa, MG, Brazil, 2015

Dietary Patterns	Excess weight		Increased WC		Increased WHtR		Increased NC		% Increased body fat	
	PR	95% CI	PR	95% CI	PR	95% CI	PR	95% CI	PR	95% CI
Unhealthy DP	0.90	(0.64-1.28)	0.79	(0.37-1.67)	0.95	(0.57-1.59)	1.26	(0.76-2.07)	1.07	(0.86-1.35)
Snacks	1.12	(0.81-1.54)	1.21	(0.62-2.35)	1.11	(0.68-1.82)	1.79	(1.13-2.85)*	0.91	(0.71-1.16)
Traditional	0.96	(0.69-1.34)	0.82	(0.42-1.59)	0.96	(0.58-1.59)	1.03	(0.60-1.76)	1.20	(0.93-1.55)
Industrialized	1.58	(1.18-2.10)*	1.73	(0.93-3.22)	1.59	(1.01-2.49)	1.44	(0.89-2.34)	1.50	(1.23-1.82)*
Healthy	0.92	(0.66-1.27)	0.72	(0.38-1.38)	1.04	(0.62-1.75)	0.94	(0.56-1.59)	0.92	(0.73-1.16)

PR: prevalence ratio; 95% CI: confidence interval; WC: waist circumference; WHtR: waist-to-height ratio. Food standard assessed through the 75th percentile. For the traditional and healthy standards, the Percentile ≥ 75 was adopted as a protection factor, for the other standards the percentile < 75 was adopted as a reference.

* Statistical significance ($p < 0.05$). Poisson regression with robust variance (bivariate).

Our findings highlight the importance of assessing dietary patterns in the population, especially in children, who may, from an early age, have inadequate eating habits that promote excess weight.^{11,23} The presence of obesity in children may increase the risk for developing cardiovascular diseases and predict health risks later in life.⁷

As limitations of our study, we can highlight the evaluation of dietary patterns through the 24-hour food recall, which may underestimate the actual consumption

of children due to memory bias and/or lack of cooperation of the interviewee. However, we emphasize that all R24h were applied by properly trained nutritionists. Moreover, the child was present with the person responsible for answering the dietary survey, since children under 12 years of age might not answer accurately regarding food intake information.

Some strong points of this study should be highlighted. This is one of the few studies in developing countries that

adiposity in childhood. As the consumption of industrialized foods contributes to excess weight and body fat, this is an important step in assessing dietary patterns, since diet is a modifiable risk factor for cardiovascular disease. These findings are consistent with other studies, suggesting that the consumption of industrialized foods is increasing, and these are already associated with cardiometabolic alterations in the early stages of life, such as in childhood.

Conclusion

It was concluded that the prevalence of excess weight and body adiposity were higher in children with greater adherence to the industrialized DP. The lower consumption of the traditional DP was associated with excess body adiposity. Our study suggests that early assessments of eating habits should be undertaken for monitoring and modifying these habits, when necessary. Parents and health professionals need to be aware of the high consumption of processed and ultra-processed products by children. Food and nutritional educational actions become of the utmost importance in schools as a way to reinforce the healthy diet of children and their parents.

Author contributions

Conception and design of the research and Obtaining financing: Novaes JF; Acquisition of data: Rocha N,

Milagres LC, Filgueiras MS, Silva MA, Albuquerque FM; Analysis and interpretation of the data: Rocha N, Ribeiro AQ, Albuquerque FM, Novaes JF; Statistical analysis: Rocha N, Filgueiras MS; Critical revision of the manuscript for intellectual content: Milagres LC, Filgueiras MS, Suhett LG, Silva MA, Ribeiro AQ, Vieira SA, Novaes JF.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by CNPq.

Study Association

This article is part of the thesis of Doctoral submitted by Naruna Pereira Rocha, from Universidade Federal de Viçosa.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Universidade Federal de Viçosa under the protocol number 663.171/2014. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

- Hassapidou M, Tzotzas T, Makri E, Pagkalos I, Kaklamanos I, Kapantais E, et al. Prevalence and geographic variation of abdominal obesity in 7- and 9-year-old children in Greece; World Health Organization Childhood Obesity Surveillance Initiative 2010. *BMC Public Health*. 2017;17(1):126.
- World Health Organization (WHO). Report of The Commission on Ending Childhood Obesity. Geneva: WHO Library Cataloguing-in-Publication Data, 2016, p. 50.
- Brasil. Instituto Brasileiro de Geografia e Estatística. Pesquisas de orçamentos familiares: antropometria e estado nutricional de crianças, adolescentes e adultos no Brasil. Rio de Janeiro: 2010.
- Oellingrath IM, Svendsen MV, Brantsæter AL. Eating patterns and overweight in 9- to 10-year-old children in Telemark County, Norway: a cross-sectional study. *Eur J Clin Nutr*. 2010;64(11):1272-9.
- Lioret S, Touvier M, Lafay L, Volatier JL, Maire B. Dietary and physical activity patterns in French children are related to overweight and socioeconomic status. *J Nutr*. 2008;138(1):101-7.
- Ambrosini GL. Childhood dietary patterns and later obesity: a review of the evidence. *Proc Nutr Soc*. 2014;73(1):137-46.
- Shang X, Li Y, Liu A, Zhang Q, Hu X, Du S, et al. Dietary pattern and its association with the prevalence of obesity and related cardiometabolic risk factors among Chinese children. *PLoS One*. 2012;7(8):e43183.
- Torres Stone RA, Waring ME, Cutrona SL, Kiefe CI, Allison J, Doubeni CA. The association of dietary quality with colorectal cancer among normal weight, overweight and obese men and women: a prospective longitudinal study in the USA. *BMJ Open*. 2017;7(6):e015619.
- Livingstone KM, McNaughton SA. Dietary patterns by reduced rank regression are associated with obesity and hypertension in Australian adults. *Br J Nutr*. 2017; 117(2):248-59.
- Ambrosini GL, Emmett PM, Northstone K, Howe LD, Tilling K, Jebb SA. Identification of a dietary pattern prospectively associated with increased adiposity during childhood and adolescence. *Int J Obes*. 2012;36(10):1299-305.
- Dishchekian VRM, Escrivão MAM, Palma D, Ancona-Lopez F, Araujo EAC, Taddei JAAC. Dietary patterns of obese adolescents and different metabolic effects.. *Rev Nut Campinas*. 2011; 24(1):17-29.
- Carvalho CA, FONSECA PCA, Nobre LN, Priore SE, Franceschini SCC. Methods of a posteriori identification of food patterns in Brazilian children: a systematic review.. *Ciênc Saúde Colet*. 2016;21(1):143-54.
- Pereir SS, Alvarez-Leite JL. Low-grade inflammation, obesity, and diabetes. *Curr Obes Rep*. 2014; 3(4):422-31.
- Ritchie B, O'hara L, Taylor J. In the kitchen' impact evaluation: engaging primary school students in preparing fruit and vegetables for their own consumption. *Health Promot J Austr*. 2015;26(2):146-9.
- Brazilian Institute of Geography and Statistics.IBGE Social indicators. An analysis of the results of the 2010 Population Census universe. Studies & Research: Demographic and socio-economic information; 2015. [citado 16 nov 2016]. Disponível em:: www.ibge.gov.br/cidadesat/topwindow.htm?1.
- Magalhães EI, Pessoa MC, Franceschini SD, Novaes JF. Dietary calcium intake is inversely associated with blood pressure in Brazilian children. *Int J Food Sci Nutr*. 2017;68(3):331-8.

17. Agromídia Software Ltda. DietPro: versão 5. i. Software de avaliação nutricional e prescrição dietética. UFV. Viçosa, MG, Brasil. AS Sistema (1997).
18. de Onis M, Onyango AW, Borghi E, Siyam A, Nishida C, Siekmann J. Development of a WHO growth reference for school-aged children and adolescents. *Bull World Health Organ*. 2007;85(9):660-7.
19. Zimmet P, Alberti KG, Kaufman F, Tajima N, Arslanian S, Wong G, et al. The metabolic syndrome in children and adolescents – an IDF consensus report. *Pediatr Diabetes*. 2007;8(5):299-306.
20. Ashwell M, Hsieh SD. Six reasons why the waist-to-height ratio is a rapid and effective global indicator for health risks of obesity and how its use could simplify the international public health message on obesity. *Int J Food Sci Nutr*. 2005;56(5)(5):303-7.
21. Nafiu OO, Burke C, Lee J, Voepel-Lewis T, Malviya S, Tremper KK. Neck circumference as a screening measure for identifying children with high body mass index. *Pediatrics*. 2010;126(2):e306-e10.
22. Lohman TG. Assessing fat distribution. In: *Advances in body composition assessment*. Illinois: Human Kinetics; 1992. p. 57-63. (Current Issues in Exercise Science).
23. Rocha NP, Milagres LC, Longo GZ, Ribeiro AQ, Novaes JF. Association between dietary pattern and cardiometabolic risk in children and adolescents: a systematic review. *J Pediatr*. 2017;93(3):214-22.
24. Karatzi K, Moschonis G, Barouti AA, Lionis C, Chrousos GP, Manios Y. Dietary patterns and breakfast consumption in relation to insulin resistance in children. the healthy Growth Study. *Public Health Nutr*. 2014;17(12):2790-7.
25. Council on Communications and Media. Children, adolescents, and the media. *Pediatrics*. 2013;132(5):958-61.
26. World Health Organization (WHO). Obesity: Preventing and managing the global epidemic – Report of a WHO consultation on obesity. Geneva; 1998.
27. Souza RL, Madruga SW, Gigante DP, Santos IS, Barros AJ, Assunção MC. Dietary patterns and associated factors among children one to six years of age in a city in southern Brazil. *Cad Saúde Pública*. 2013;29(12):2416-26.
28. Food and Agriculture Organization (FAO). FAO/Infoods Density database version 2.0 (2012). Prepared by: Charrondiere UR, Haytowitz D, Stadlmayr B.
29. Olinto MAT. Padrões alimentares: análise de componentes principais. In: Kac G, Sichieri R, Gigante DP. *Epidemiologia nutricional*. Rio de Janeiro: Editora FIOCRUZ/Atheneu; 2007 [acesso 2018 dez 13] . Disponível em: <http://books.scielo.org>.
30. Durão C, Severo M, Oliveira A, Moreira P, Guerra A, Barros H, et al. Association between dietary patterns and adiposity from 4 to 7 years of age. *Public Health Nutr*. 2017;20(11):1973-82.
31. Villa JKD, Santos TSS, Ribeiro AQ, Silva AR, Sant’Ana LFR, Pessoa MC. Dietary patterns of children and socioeconomic, behavioral and maternal determinants. *Rev Paul Pediatr*. 2015;33(3):302-9.
32. Fisberg M, Tasca Del’Arco APW, Previdelli AN, Nogueira-de-Almeida CA. Consumo de bebidas por crianças brasileiras com idades entre 4 e 11 anos de idade e seu impacto na ingestão de açúcar de adição: Estudo de amostragem nacional. *Intern J Nutr*. 2016;9(2):169-81.
33. Hanks AS, Just DR, Wansink B. Chocolate milk consequences: a pilot study evaluating the consequences of banning chocolate milk in school cafeterias. *PLoS One*. 2014;9(4): e91022.
34. Rauber F, Campagnolo PD, Hoffman DJ, Vitolo MR. Consumption of ultra-processed food products and its effects on children’s lipid profiles: a longitudinal study. *Nutr Metab Cardiovasc Dis*. 2015;25(1):116-22.
35. Bezerra IN, Cavalcante JB, Moreira TMV, Mota CC, Sicheiri R. Eating away from home and excess weight: an analysis of explanatory mechanisms *Rev Bras Prom Saúde*. 2016; 29(3):455-61.
36. Bonett LP, Baumgartner MST, Klein AC, Silva LI. Compostos nutricionais e fatores antinutricionais do feijão comum (*Phaseolus vulgaris* L.). *Arq Ciênc Saúde Unipar*. 2007; 11;(3):235-46.
37. Kupek E, Lobo AS, Leal DB, Bellisle F, Assis MAA. Dietary patterns associated with overweight and obesity among Brazilian schoolchildren: an approach based on the time-of-day of eating events. *Br J Nutr*. 2016; 116(11):1954-65.
38. Zhang J, Wang H, Wang Y, Xue H, Wang Z, Du W, et al. Dietary patterns and their associations with childhood obesity in China. *Br J Nutr*. 2015;113(12):1978-84.



Dietary Patterns and Healthy Habits Along the Life Course

Lucia Campos Pellanda 

Universidade Federal de Ciências da Saúde de Porto Alegre - Saúde Coletiva, Porto Alegre, RS – Brazil

Instituto de Cardiologia / Fundação Universitária de Cardiologia (IC/FUC), Porto Alegre, RS – Brazil

Short Editorial related to the article: Association of Dietary Patterns with Excess Weight and Body Adiposity in Brazilian Children:

The Pase-Brasil Study

Childhood represents a critical window in the life course for the establishment of dietary patterns and other healthy habits. In the last decades, these habits have been changing significantly, and childhood obesity has become an increasing public health issue, with many clinical consequences.¹⁻³

To address these issues, it is of paramount importance to understand dietary patterns and their relation to body measurements, as Rocha et al propose in the paper “Association of Dietary Patterns with Excess Weight and Body Adiposity in Brazilian Children: The Pase-Brasil Study.”⁴ The authors have identified five different patterns, including the “traditional Brazilian”, “non-healthy”, “fast-food/snacks”, “processed” and “healthy”.

The study of eating patterns is extremely complex, as all behavioural factors that contribute to multifactorial chronic disease. They may be influenced by and subject to many confounding factors and interactions, especially with physical activity patterns, cultural patterns, socio-economical variables, gender, urbanisation, food practices, parenting styles and other psychological variables. The authors controlled for some important variables, such as sedentary behaviour and maternal body mass index. It's noteworthy that almost 75% of children presented with sedentary behaviour and almost 60% of mothers had excess weight, thus, the interactions of all these variables must be carefully considered. All these complexities and difficulties in analysing dietary patterns in childhood make this study more valuable, and the discussion must advance further to include other important variables.

The five categories proposed in the study are useful for the purpose of epidemiological studies, but one must be very careful to transpose these categories to clinical recommendations. It is important to highlight that there is a spectrum of healthy to non-healthy habits, thus, naming one of these patterns as healthy, and other as non-healthy may not be so useful clinically, when they are more complex and composed by healthy and unhealthy foods in different proportions.

The traditional Brazilian pattern, for example, is considered healthy by the Brazilian dietary guidelines.⁵ Although the traditional pattern may be not ideal, with a high intake of salt and sugar, the results of the present paper show that the less this pattern was consumed, the greater prevalence of excess weight.

This is very interesting and adds to the knowledge we have already accumulated about Brazilian and other Latin-America traditional dietary patterns. Although for many decades these patterns were overlooked and sometimes considered unhealthy, they were more recently linked with low rates of obesity and chronic diseases.⁶ Of course that many more lifestyle changes have happened simultaneously, but it is very important to consider the relationship between interpretation of previous findings and the marketing of processed foods in these countries, with possible conflicts of interest in industry-funded research. Some decades ago, breastfeeding was considered insufficient feeding for newborn babies and artificial formulae was marketed to paediatricians and families as the most healthy options.^{7,8} The same may have happened to traditional food patterns that are culturally accepted by gradually have been substituted for “modern” processed alternatives.

According to the Brazilian guidelines, the most deleterious pattern is the one that includes mainly ultra-processed foods. This seems to be in accordance with the results that were found in the present study, where the group with a greater prevalence of obesity was the “industrialized group”.

To add to the complexity, the “unhealthy” pattern contains foods that are healthy and recommended for this age group, as the authors describe very well, such as milk, but mostly in unhealthy preparations.

It is very important that we begin to discuss these patterns with more detail to reach better standardisation, allowing international comparisons and a greater understanding of the relations of these patterns with other healthy habits. A recent systematic review pointed out the difficulty of standardisation and the need for a common tool to evaluate dietary intake.⁹

Due to the multifactorial characteristics of childhood obesity, comprehensive interventions that include nutrition education programs and physical activity in multidisciplinary approaches are needed. Evidence is constantly evolving, and guidelines are changing regarding quantitative and qualitative variables, such as certain types of foods or intensity of physical activity. Best results are achieved when multiple actors and scenarios are involved, including family, school, groups, social media, and health professionals and services.¹⁰

Keywords

Healthy Diet; Diet Western; Risk Reduction Behavior; Acculturation; Exercise; Social Class; Multiple Chronic Conditions.

Mailing Address: Lucia Campos Pellanda •

UFCSPA Av. Sarmento Leite, 245. Postal Code 90050-170, Porto Alegre, RS – Brazil

E-mail: pellanda@ufcspa.edu.br

DOI: 10.5935/abc.20190127

References

1. Pires A, Martins P, Pereira AM, Silva PV, Marinho J, Marques M, et al. Insulin resistance, dyslipidemia and cardiovascular changes in a group of obese children. *Arq Bras Cardiol.* 2015;104(4):266-73.
2. Moraes LI, Nicola TC, Jesus JS, Alves ER, Giovaninni NP, Marcato DG, et al. High blood pressure in children and its correlation with three definitions of obesity in childhood. *Arq Bras Cardiol.* 2014;102(2):175-80.
3. Ferreira AP, Ferreira CB, Brito CJ, Pitanga FJ, Moraes CF, Naves LA, et al. Prediction of metabolic syndrome in children through anthropometric indicators. *Arq Bras Cardiol.* 2011;96(2):121-5.
4. Rocha N, Milagres LC, Filgueiras MR, Suhett LG, Silva MA, Albuquerque FM, et al. Associação dos Padrões Alimentares com Excesso de Peso e Adiposidade Corporal em Crianças Brasileiras: Estudo Pase-Brasil. *Arq Bras Cardiol.* 2019; 113(1):52-59
5. Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Departamento de Atenção Básica [internet]. Guia alimentar para a população brasileira. 2. ed. Brasília: Ministério da Saúde; 2014.[acesso em 02 jun 2019]. Disponível em: http://bvsms.saude.gov.br/bvs/publicacoes/guia_alimentar_populacao_brasileira_2ed.pdf
6. Monteiro CA, Cannon G. The impact of transnational “big food” companies on the South: a view from Brazil. *PLoS Med.* 2012;9(7):e1001252.
7. Kaplan DL, Graff KM. Marketing breastfeeding--reversing corporate influence on infant feeding practices. *J Urban Health.* 2008;85(4):486-504.
8. Lutter CK, Chaparro CM, Grummer-Strawn L, Victora CG. Backsliding on a key health investment in Latin America and the Caribbean: the case of breastfeeding promotion. *Am J Public Health.* 2011;101(11):2130-6.
9. Leme ACB, Fisberg RM, Thompson D, Philippi ST, NicklasT, Baranowski T. Brazilian children's dietary intake in relation to Brazil's new nutrition guidelines: a systematic review. *Curr Nutr Rep.* 2019;8(2):145-66.
10. Sbruzzi G, Eibel B, Barbiero SM, Petkowicz RO, Ribeiro RA, Cesa CC, et al. Educational interventions in childhood obesity: a systematic review with meta-analysis of randomized clinical trials. *Prev Med.* 2013;56(5):254-64.



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

The Profile of the Brazilian Cardiologist – A Sample of Members of the Brazilian Society of Cardiology

Lucas Simonetto Faganello,¹ Mauricio Pimentel,¹ Carisi Anne Polanczyk,¹ Tiago Zimmerman,¹ Marcus Vinicius Bolivar Malachias,² Oscar Pereira Dutra,³ Leandro Ioschpe Zimmerman¹

Hospital de Clínicas de Porto Alegre,¹ Porto Alegre, RS – Brazil

Faculdade de Ciências Médicas de Minas Gerais,² Belo Horizonte, MG – Brazil

Instituto de Cardiologia – Fundação Universitária de Cardiologia do Rio Grande do Sul,³ Porto Alegre, RS – Brazil

Abstract

Background: Data from the international literature have shown changes in the profile of cardiologists and in their medical practices. However, there is no data on this in Brazilian cardiologists.

Objective: To evaluate professional and personal characteristics of a sample of Brazilian cardiologists.

Methods: This was a cross-sectional study; a questionnaire was sent by e-mail to cardiologists, active members of the Brazilian Society of Cardiology in 2017. The results were analyzed, and the level of significance set at $p < 0.05$.

Results: The questionnaire was sent to 13,462 cardiologists, with 2,101 (15.6%) respondents, mostly men (71.8% versus 28.2%). Age distribution and marital status were significantly different between the sexes ($p < 0.001$). The number of cardiologists without children was higher among women (40.5% versus 16.1%; $p < 0.001$). The most common place of work was the public hospital (46.5%), followed by private hospital (28.5%) and private office (21.1%). The office was the main place of work for 23.9% of men and 14% of women ($p < 0.001$), with predominance of individuals older than 50 years (31.7% versus 10.1%, respectively; $p < 0.001$). Most cardiologists (64.2%) worked more than 40 hours a week (69% of them men and 51.9% of the women; $p < 0.001$). Eighty-eight percent of the sample earned more than BRL 11,000 (US\$ 3,473.43), and 66.5% of the men earned more than BRL 20,000 (US\$ 6,315.32) per month, versus 31.2% of the women ($p < 0.001$). A high level of work-related stress was reported by 11.3% of respondents.

Conclusion: Most cardiologists were men, who showed higher workload and higher income; 11.3% of the cardiologists perceived stress as a great deal. (Arq Bras Cardiol. 2019; 113(1):62-68)

Keywords: Cardiologists; Survey and Questionnaires; Income; Gender; Demographic Data; Quality of Life.

Introduction

Medical activity has been associated with high levels of stress and dissatisfaction compared with other occupations.¹ Previous studies have shown that there is a complex relationship between the level of work satisfaction, work-life balance, burnout level, demographic factors and work conditions.²

The progress of medicine and specialties, especially in the last decades, has promoted rapid changes in personal and professional lives of cardiologists.³⁻⁵ In addition, international data have shown the aging of working classes, with changes in the profile and characteristics of professional activities, but still a predominance of men and a striking difference of salaries between the sexes.⁶

However, data on the profile of Brazilian cardiologists and their perceptions of the profession are limited.

Therefore, the present study describes the profile of the Brazilian cardiologist from data obtained in the study conducted by the Brazilian Society of Cardiology (BSC), in terms of demographic, social, and professional aspects and quality of life.

Methods

The BSC developed a questionnaire composed of three main domains: demographic data, professional activity and quality of life. This questionnaire was sent by e-mail to 13,462 cardiologists, active members of the BSC in 2017. A total of 2,101 participants answered the questionnaire and composed the study group, 1,509 men (71.8%) and 592 women (28.2%).

Statistical analysis

The variables were expressed as absolute frequency, percentage and 95% confidence interval. Qualitative variables were compared using the chi-square test followed by analysis of adjusted standardized residuals. Analysis of the answers was performed using the SPSS Statistics for Windows version 25.0 (IBM, Chicago). The level of significance was set at 5% ($p < 0.05$).

Mailing Address: Leandro Ioschpe Zimmerman •

Hospital de Clínicas de Porto Alegre - Ramiro Barcelos, 2350. Postal Code 90035-903, Porto Alegre, RS – Brazil

E-mail: zimmerman@cardiol.br, lizimmerman@gmail.com

Manuscript received September 12, 2018, revised manuscript October 10, 2018, accepted November 01, 2018

DOI: 10.5935/abc.20190089

Results

Demographic data

Of the 13,462 active members of the BSC, 9,555 (70.9%) were men, 9,752 (71.1%) were aged between 30 and 59 years, and 1,323 (9.8%) aged 70 years or older. Most members lived in the southeast (55.5%) or in the south (15.1%) of Brazil as follows – 3,420 (25.4%) in São Paulo, 2,158 (16%) in Rio de Janeiro, 1,572 (11.6%) in Minas Gerais, 853 (6.3%) in Rio Grande do Sul and 774 (5.7%) in Paraná State.

The questionnaire was answered by 2,101 cardiologists (response rate 15.6%), 1,509 men (71.8%) and 592 women (28.2%). Regarding the age of participants, 1,077 (51.3%) were older than 50 years. Figure 1 shows the distribution of age by sex, with a difference between men and women ($p < 0.0001$). Thirty-four percent of men and 13% of women were aged 60 years or older. Most respondents were married (77.7%), 84.7% of the men and 59.8% of the women ($p < 0.001$). With respect to the number of children, 23% did not have children, and 57.3% had two or more children. The number of cardiologists who did not have children was higher among women (40.5 versus 16.1%; $p < 0.001$). The difference remained significant after adjustment for age, but not after adjustment for marital status.

Characteristics of professional activity

Most respondents (70.5%) had the title of specialists in cardiology from the BSC/Brazilian Medical Association, and 29.5% were applicants for the title. Most participants ($n = 1,336$; 65.4%) worked in only one field, especially clinical cardiology (50.5%), with no difference between men and women; 2.8% of the interviewees did not answer this question.

Regarding the number of working hours per week, 1,350 (64.2%) participants (69% of the men and 51.9% of the women, $p < 0.001$) worked more than 40 hours; 363 (17.3%) worked in only one place, and 1,036 (49.3%) worked in three or more places. The most common place of work was the public hospital (46.5%), followed by private hospital (28.5%) and private office (21.15) (Figure 2). The public hospital was the main place of work for 53% of women 44% of men ($p < 0.001$). On the other hand, private office was the main work place for 23.9% of men and 14% of women, three times more frequent among cardiologists older than 50 years (31.7 versus 10.1%). Only 0.3% of participants reported to work in public health centers. No difference was found in the number of work places between the sexes.

Monthly income was higher than 11,000 Brazilian reals (BRL) (US\$ 3,473.43). The distribution of income by sex is depicted in Figure 3; 66.5% of men and 31.2% of women ($p < 0.001$) reported to gain more than 20,000 BRL (adjusted for number of working hours and age range).

Regarding the level of stress (Figure 4), 64.2% reported an adequate level of stress; 11.3% perceived stress as a great deal, and 24.3% reported no stress. The causes of stress at work were poor working conditions (36.7%), excessive working hours (23.5%), low pay (15.7%), work pressure (10.9%), and others (13%).

With regards to legal issues, 13.9% of participants reported having been sued for medical malpractices, and 0.3% reported to have been condemned. The question was not answered by 10 participants (0.4%).

Considering the age participants wished to retire, 10.5% reported they wished to retire before the age of 60 years, 46.1% between 61 and 70 years, 34.1% between 71 and 80 years, 4.7% older than 80 years, and 14.6% reported they do not want to retire from their work as a cardiologist. Regarding the retirement financial planning, 58.4% reported to contribute to a private retirement plan.

The questionnaire also included questions about participants' perception on the influence of technology, spirituality, the role of the media on their work. The use of technology on a daily basis was reported by 84.7% of the respondents, with no difference between sexes and age ranges. The frequency of technology use for patient-physician communication was daily for 40.6% and weekly for 21.7% of participants. Regarding the role of spirituality in the treatment of the patients, it was considered "very useful" by 54.7%, "useful" by 30.1%, "not very useful" by 6% of the respondents; 9.1% did not have a strong opinion about the issue, and 0.5% did not answer the question. In terms of the frequency the physicians talked about the subject "spirituality" with their patients, 54.1% answered "eventually", 24.5% "often", 14.2% "never" and 0.5% did not answer the question. As for how medical work was presented by the media, 73.7% considered that the opinion expressed by the media was partial and unfavorable to the doctors.

Quality of life

Most cardiologists reported to sleep between 6 and 7 hours per night (79.5%), with no differences between men and women. Considering the time dedicated to family and leisure activities (Figure 5), 41.8% answered less than 10 hours per week; 29.8% between 11 and 20 hours per week, 17.9% between 21 and 30 hours per week, and 10.4% 31 hours or more per week. The proportion of women who spent more than 20 hours with family-related and leisure activities was greater than that of men (33.4% versus 26.2%; $p < 0.001$).

Smoking habit was reported by only 2.8% of cardiologists (3.3% of men and 1.5% of women, $p = 0.03$). Regarding alcohol consumption, 34.3% reported the frequency of ≥ 2 times (40.1% of the men and 19.5% of the women, $p < 0.001$), 30.1% sometimes a month, 23.4% rarely, and 12% never. Regarding health-related self-care, 52.6% considered themselves to be careful, 7.9% very careful, and 3.4% not careful, with no difference between men and women. With respect to the health of participants, 56.1% reported to have a disease (42.5% of the men and 63.3% of the women; $p < 0.001$). Sixty percent reported continuous use of medication (57.3% of the men and 59.1% of the women, $p = 0.46$).

Discussion

This is the third time the BSC developed studies aimed at evaluating the profile of its member associates. However, this is the first time the Society promoted a more comprehensive study and published the results.

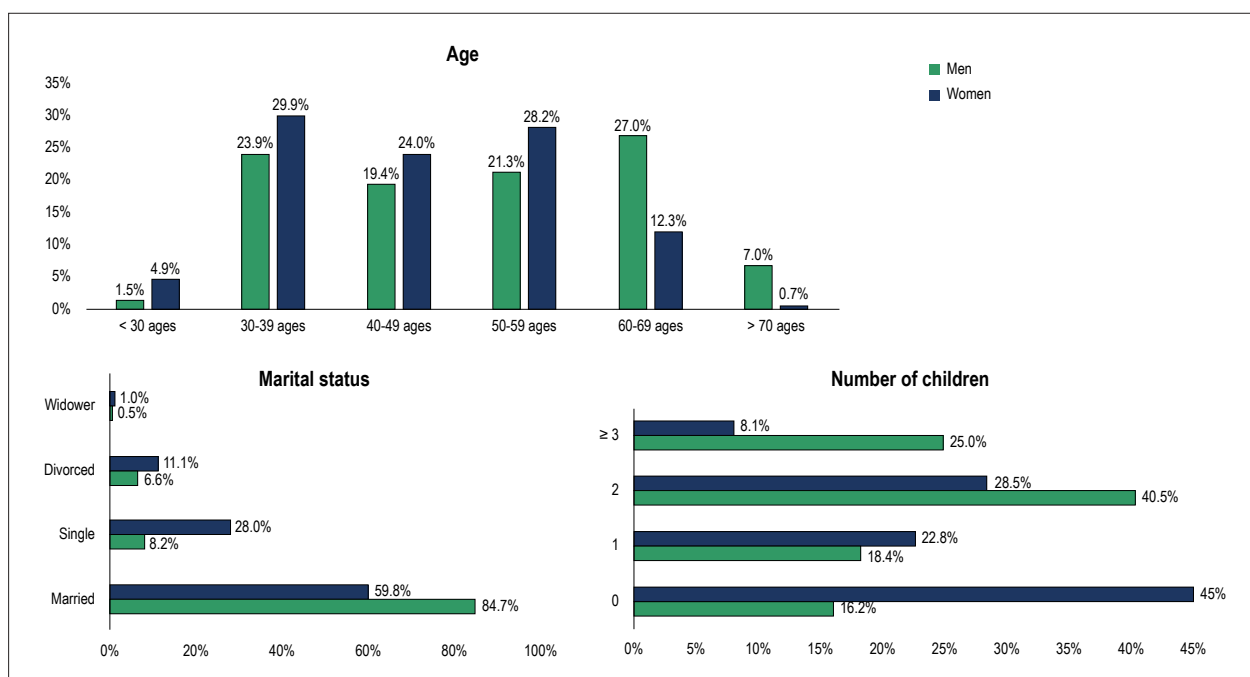


Figure 1 – Demographic characteristics.

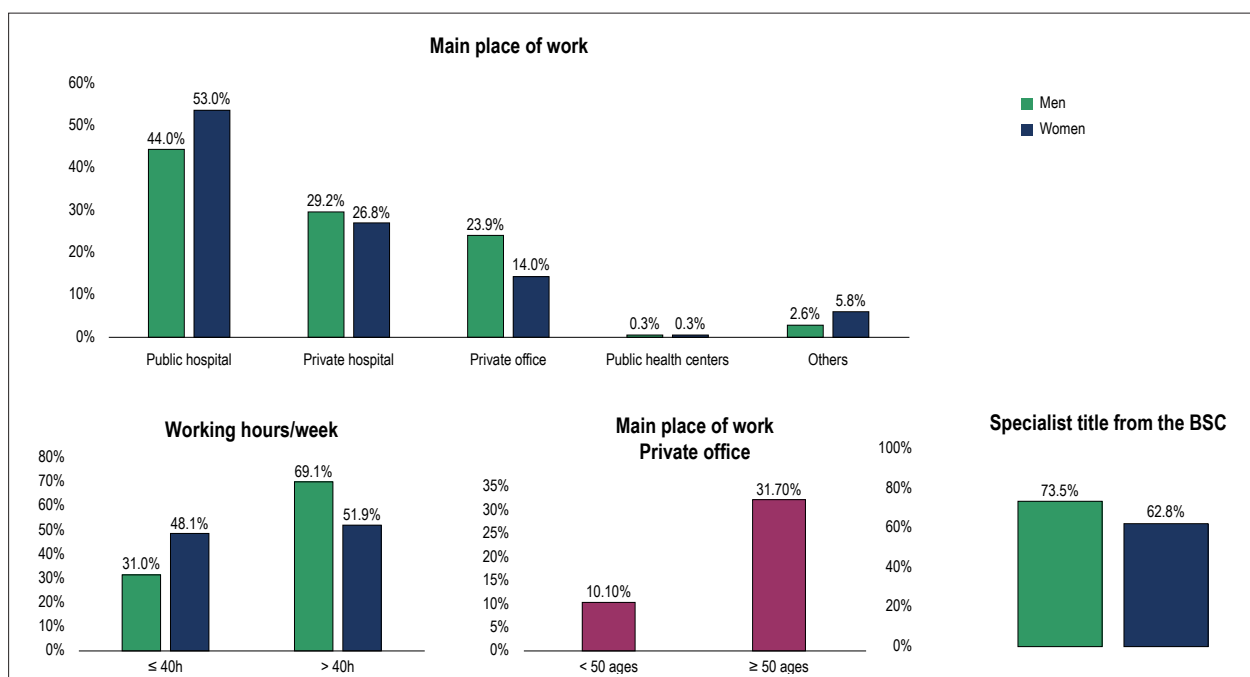


Figure 2 – Professional characteristics. BSC: Brazilian Society of Cardiology

Despite the increase of women among medical professionals,⁷ there is a remarkable predominance of men among Brazilian cardiologists, similar to what is observed in other countries.^{6,8,9} Most respondents in our study was men (71.8% versus 28.2%), which is in agreement with the 2018 medical demography in Brazil,⁷ showing a

distribution of 69.7% of and 30.3% of women, and mean age of 48.9 ± 12.1 years among Brazilian cardiologists. This difference is greater among cardiologists older than 50 years and less pronounced in younger subjects. Differences between sexes were observed for marital status, number of children, income and workload.

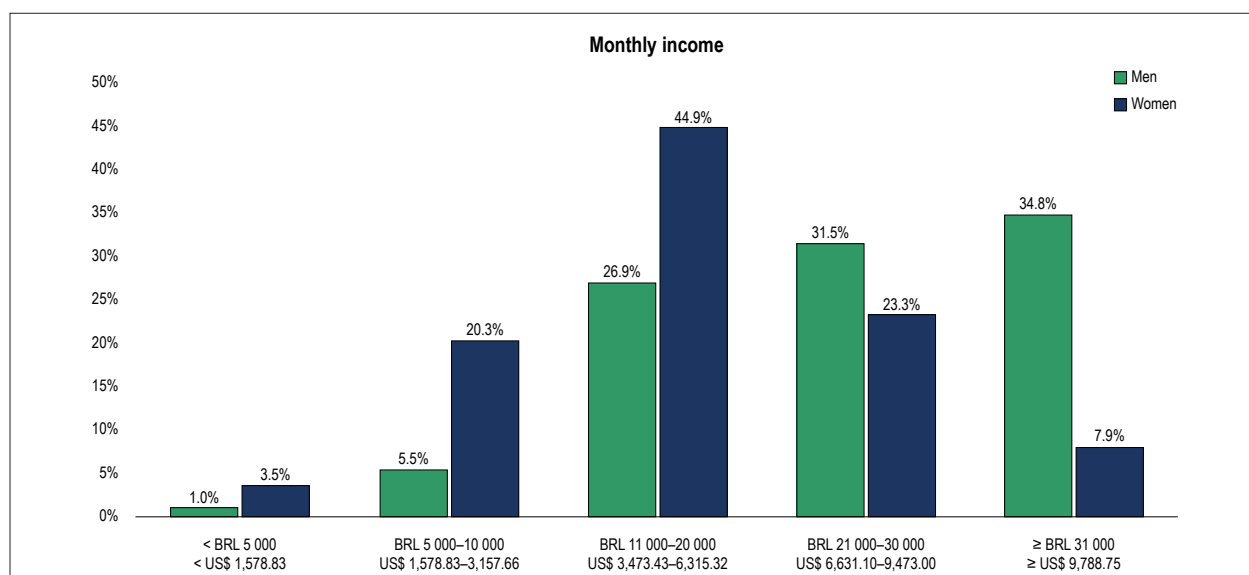


Figure 3 – Salary difference between men and women.

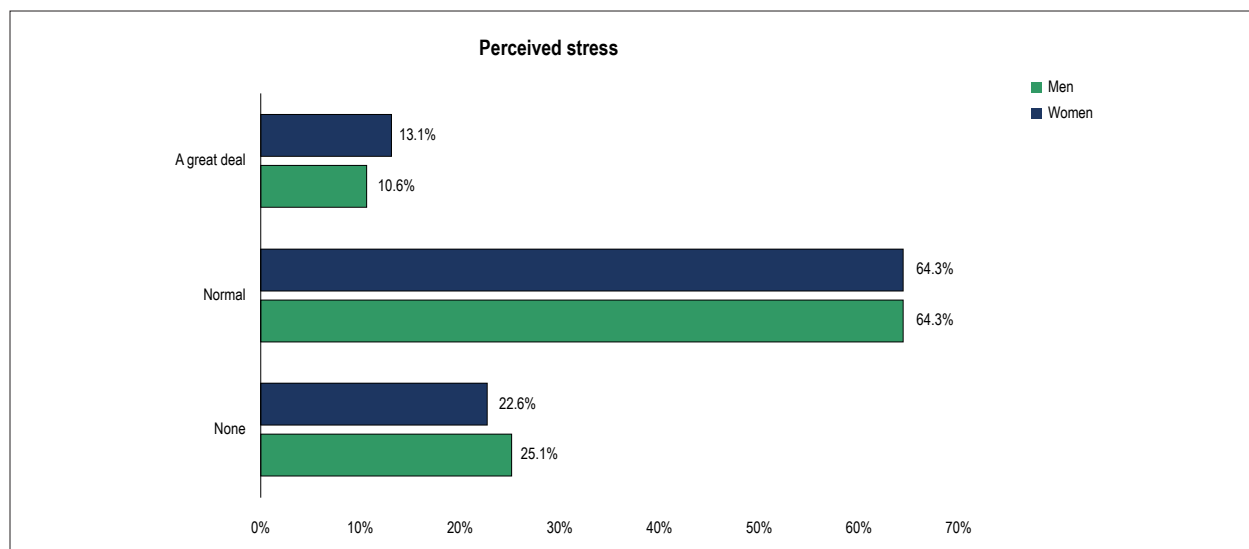


Figure 4 – Level of stress.

The proportion of married men who answered the questionnaire was significantly higher than that of women. The proportion of cardiologists who did not have children was higher among women, even after adjustment for age. Such difference is in accordance with the results of a study conducted with North-American cardiologists.⁶ Therefore, it is possible to infer that the prolonged time from graduation and specialization may be associated with these findings.

Our study showed that, in higher income ranges, the proportion of men was higher than of women, adjusted for work load and number of workplaces. This difference in income between sexes has been reported in several other professional sectors⁵ and has been registered in

the last decades among North-American cardiologists. Most professionals reported to work more than 40 hours a week, with higher proportion of men in the private sector. The proportion of women was higher in the public and academic settings, in which a lower income was identified as compared with the private setting.

Almost half of cardiologists work in three or more places. Interestingly, the private office was reported to be the main place of work by only 21.1% of the respondents, and this rate was even lower when considering individuals younger than 50 years only. Thus, cardiology practice in private sectors has been less commonly seen probably due to elevations in the number of doctor visits covered by private health

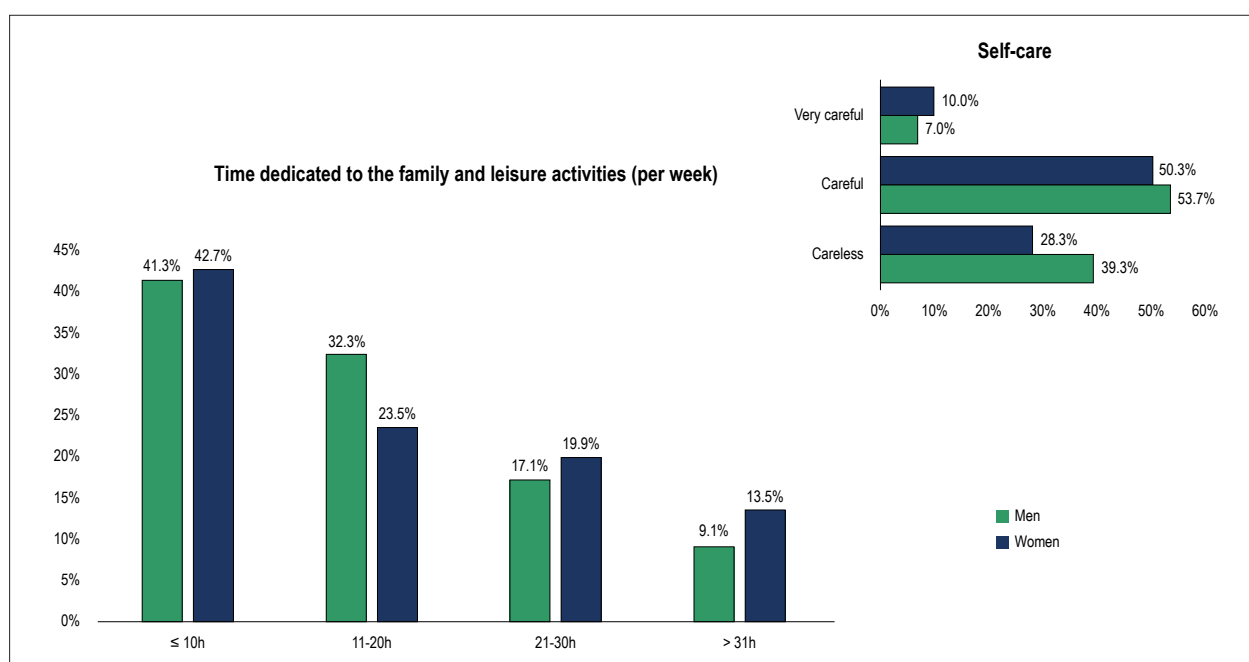


Figure 5 – Quality of life.

plans. These plans pay a relatively low price per service to the physicians, who feel discouraged to set up and maintain their own clinics. This change in the professional scenario may also be related to the fact that younger cardiologists are concerned not only about seeking more immediate revenue but also about investing in complementary pension.

Despite the high work load, only 11.3% of cardiologists perceived stress as a great deal. A study published by Mescape¹⁰ concluded that 46% of North-American cardiologists had symptoms of burnout, similar to the frequency reported in other specialties like pneumology and nephrology. Although the questionnaire used in the study did not include specific criteria for the diagnosis of burnout, data have suggested that there are considerable differences between Brazilians and North-Americans regarding the perception of stress at work, which can be related to sociocultural differences. Also, there is a relatively lower occurrence of medical lawsuits among Brazilian cardiologists. While 0.3% of our sample reported having been condemned, a study published in the American Heart Journal in 2014¹¹ reported a rate of malpractice lawsuits of 8.6% in North America and a 1% condemnation rate.

The practice of physical exercise has well-established cardiovascular benefits and should be encouraged. In our study, however, 31% of cardiologists did not practice exercise. Only 11% of North-American cardiologists reported to be physically inactive.¹⁰ This difference may be due to the higher workload faced by physicians in Brazil. Although the percentage of smokers was relatively low, a high percentage of cardiologists reported they were careless about their health (39.4%). Regarding alcohol consumption,

34.3% of respondents reported a frequency of two times a week or more; 49% of North American cardiologists consumed up to one drink per week. These data indicate that institutional campaigns aimed at promoting the adoption of healthy habits and self-care among Brazilian cardiologists should be considered.

The use of technology has facilitated the search for knowledge and contributed in different aspects of daily life; also, it has allowed patients to communicate more directly with their doctors. In our study, most cardiologists reported to use any kind of technology on a daily basis in their work. A significant percentage (40.6%) of cardiologists is contacted daily by patients through technology device, which adds to the debate about the availability of physicians to respond to patients' emails or on social media.

According to the Brazilian Medical Council's resolution, published in 2002,¹² despite numerous positive consequences of telemedicine, it is related to serious ethical and legal issues. Considering the exponential use of social media by physicians, including for patient-doctor communication, the Medical Council, in 2017,¹³ recognized the importance of the social media and established rules of conduct in this context.

There has been increasing interest in issues of spirituality in the medical practice. In the BSC, a group of study on spirituality and cardiovascular medicine was created. In the present study, although 54.7% of participants considered that spirituality was very useful in the treatment of the patients, 14.2% has never talked about this subject with their patients and most (54.1%) of them did it only eventually. This difference may be related to the scarcity of validated qualification in the area.

The study has some limitations, particularly regarding data collection. The rate of response to the questionnaire was relatively low (15.6%), and on this basis, we cannot affirm that the results would be the same in a larger sample. However, similar studies have shown comparable results (15-25%). In the most recent study conducted by the American College of Cardiology, which has continuously developed studies on the theme in the last three decades, the response rate was 21%. In the study conducted by the Medscape, the rate of response was 4%.

Conclusion

In this original study on the profile of Brazilian cardiologists, associates of the BSC, significant differences between sexes were detected. While men had a greater work load, the participation of women in higher income ranges was lower, even after adjustment for work load. Most cardiologists worked in more than one place, mostly in the public sector. Younger cardiologists had a lower tendency to work in private offices. The perception of the level of work-related stress was considered satisfactory. Considering the growing concern over personal and professional quality of life, as well as over work performance, future research is warranted to further explore the theme and to allow the planning of actions by medical entities and societies, so that the specialty of cardiology can continue to attract the interest of medical professionals.

Acknowledgements

The questionnaire was developed and administered during the 2016-2017 term. For this reason, we thank the board of directors: Eduardo Nagib Gaui, Glaucia Maria Moraes de Oliveira, Raul Dias dos Santos Filho, Denilson

Campos de Albuquerque, Walter José Gomes, Celso Amodeo, Osni Moreira Filho, Renault Mattos Ribeiro Junior, José Luiz Aziz, João David de Souza Neto and Weimar Kunz S. Barroso de Souza.

Author contributions

Conception and design of the research: Malachias MVB, Dutra OP, Zimmerman LI; Analysis and interpretation of the data: Faganello LS, Pimentel M, Polanczyk CA, Malachias MVB, Dutra OP, Zimmerman LI; Statistical analysis and Writing of the manuscript: Faganello LS, Pimentel M; Critical revision of the manuscript for intellectual content: Faganello LS, Pimentel M, Polanczyk CA, Zimmerman TI, Malachias MVB, Dutra OP, Zimmerman LI.

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 Lucas Simonetto Faganello, from Universidade Federal do Rio Grande do Sul.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Shanafelt TD, Boone S, Tan L, Dyrbye LN, Sotile W, Satele D, et al. Burnout and satisfaction with work-life balance among US physicians relative to the general US population. *Arch Intern Med*. 2012; 172(18):1377-85.
2. Keeton K, Fenner DE, Johnson TRB, Hayward RA. Predictors of physician career satisfaction, work-life balance, and burnout. *Obstet Gynecol*. 2007; 109(4):949-55.
3. Limacher MC, Zaher CA, Walsh MN, Wolf WJ, Douglas PS, Schwartz JB, et al. The ACC professional life survey: career decisions of women and men in cardiology. A report of the Committee on Women in Cardiology. American College of Cardiology. *J Am Coll Cardiol*. 1998;32(3):827-35.
4. Michel JB, Sangha DM, Erwin JP. Burnout among cardiologists. *Am J Cardiol*. 2017; 119(6):938-40.
5. Tsukada YT, Tokita M, Kato K, Miyauchi M, Ono I, Tanabe H, et al. Solutions for retention of female cardiologists: from the survey of gender differences in the work and life of cardiologists. *Circ J*. 2009;73(11):2076-83.
6. Smith F, Labert TW, Pitcher A, Goldacre MJ. Career choices for cardiology: cohort studies of UK medical graduates. *BMC Med Educ*. 2013 Jan25;13:10.
7. Lewis SJ, Mehta LS, Douglas PS, Gulati M, Limacher MC, Poppas A, et al. American College of Cardiology Women in Cardiology Leadership Council. Changes in the Professional Lives of Cardiologists Over 2 Decades. *J Am Coll Cardiol*. 2017; 69(4):452-62.
8. Scheffer M, Cassenote A, Guillaux AG. Demografia médica no Brasil 2018. São Paulo, SP: FMUSP/ CFM/ Cremesp; 2018.
9. Timmis AD, English, KM. Women in cardiology: a UK perspective. *Heart*. 2005; 91(3):273-4.
10. Instituto Brasileiro de Geografia e Estatística (IBGE). [Citado em 2017 jan 12]. Disponível em: <https://agenciadenoticias.ibge.gov.br/agencia-noticias/2012-agencia-de-noticias/noticias/20234-mulher-estuda-mais-trabalha-mais-e-ganha-menos-do-que-o-homem.html>.
11. Medscape Cardiology. Medscape Cardiologist Lifestyle Report 2018: Personal Happiness vs Work Burnout. [Cited in 2018 Dec 15 Available from:] <https://www.medscape.com/slideshow/2018-lifestyle-cardiologist-6009219>.
12. Brasil. Conselho Federal de Medicina (CFM - Brasil). Resolução nº 1.643. Define a prestação de serviços através da telemedicina. *Diário Oficial da União*, 26 de agosto de 2002, Seção 1. P.205.
13. Brasil. Conselho Federal de Medicina (CFM - Brasil). Parecer nº 14/2017. Assunto: Uso do WhatsApp em ambiente hospitalar. Brasília; 2017.



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

Profile of Brazilian Cardiologists: An Overview of Female Leadership in Cardiology and Stress – Challenges for the Next Decade

Evandro Tinoco Mesquita,^{1,2,3,4} Eduardo Thadeu de Oliveira Correia,^{2,10} Letícia Mara dos Santos Barbeta^{2,9}

Sociedade Brasileira de Cardiologia - Diretoria de Qualidade Assistencial,¹ Rio de Janeiro, RJ – Brazil

Universidade Federal Fluminense,² Niterói, RJ – Brazil

Hospital Pró-Cardíaco,³ Rio de Janeiro, RJ – Brazil

Short Editorial related to the article: The Profile of the Brazilian Cardiologist – A Sample of Members of the Brazilian Society of Cardiology

Cardiology is a medical specialty that often involves outpatient and hospital activity, leading cardiovascular care in a complex setting with aging. Increasing levels of complex decision-making and knowledge about technological resources can generate overload of activities and changes in the profile of Brazilian cardiologists, such as in their compensation, free time and stress levels. As such, medical demography studies are key to understanding the dynamics of these healthcare professionals.

In the study by Faganello et al.,¹ the authors investigated the profile of Brazilian cardiologists in a cross-sectional study conducted in 2017, based on questionnaires sent by e-mail to fellow cardiologists of the Brazilian Society of Cardiology (SBC) who have been paying their membership fees regularly. Worth noting is that the likelihood of cardiologists with lower incomes not paying their membership fees is something that could generate bias in the study, thus influencing the results on their income. In addition to that, the study does not include anyone who has been exercising their professional activity without being members of SBC.

Of the 13,462 associates who pay their fees regularly, 70.9% are males, which is similar to the 2018 medical demographics published by the Brazilian Federal Council of Medicine, which identified 15,516 cardiology specialists, of which 70.1% were males, revealing that there is no significant difference between men and women joining SBC.^{1,2} Despite the significant difference between the percentage of female and male cardiologists, in the study concerned, women represented the largest share of the youngest age groups, which may reveal an increase in the number of women joining the cardiology community in recent years.¹

One of the main findings of the study was the wage difference between males and females. In the higher age groups, there was a higher proportion of men (66.5% of the men reported earning more than BRL 20,000 vs. 31.2% of women), with $p < 0.001$, even after adjusting for working hours and age group.¹ According to the article, a possible factor for this wage difference is the largest proportion of men working

in the private sector (14% of women vs. 23.9% of men), while the proportion of women in the public and academic sectors, which offer lower pays compared to the private sector, was higher (53% of women vs. 44% of men).¹ However, other factors should be considered.³ A study conducted by Douglas et al.⁴ reported that factors such as the existence of positive female models and a female-friendly specialty influence female career choices. As such, the discrepancy between the very proportion of men and women can be a factor that deter women from engaging in cardiology, in addition to the fact that there are still few women in leadership positions.

Another important aspect to be addressed, but it is not investigated in the study, is the presence of sexism in cardiology, which may be one of the factors that contribute to the lower presence of women in the specialty and their lower compensation. British studies have revealed that about 6% of the residents in the first years of specialization have experienced or witnessed sexist language, but this number rises to 15% in the last years of residence.³ In view of the above, approaches that seek to stop sexism at the workplace could lead to greater inflows of women in cardiology, encouraging them to move up their career ladder and take leadership positions, thus generating successful female models and better compensation profiles.

Another relevant finding of the study was the level of stress among cardiologists: 64.2% believe they have adequate levels of stress, 24.3% do not consider themselves stressed and 11.3% report stress to a great extent, which is mostly caused by poor working conditions. These data were significantly lower than the North American data, where burnout was present in 46% of cardiologists.¹ Although this information is important, structured tools for burnout research should be implemented in future questionnaires on the prevalence of this syndrome in Brazilian cardiologists. The study also found a high percentage of cardiologists who report being careless with their own health (39.4%) and who do not perform any type of physical activity (31%), which contrasts with the US data, where only 11% of cardiologists do not perform any physical activity.¹

In a modern and increasingly egalitarian world, it is of great relevance to discuss the factors that potentially lead to wage discrepancy between genders and the low inflow of women into the cardiology community. Awareness-raising activities and female healthcare and organizations and medical societies focused on reducing sexism, encouraging the participation of women in cardiology, and the education of female leaders are key to changing this scenario. The Brazilian Society of Cardiology, since it was founded 76 years ago, it has had 57 presidents, of which only two of its main representatives

Keywords

Cardiologists; Leadership; Salaries and Fringe Benefits; Women; Gender Identity; Sexism; Prejudice.

Mailing Address: Letícia Mara dos Santos Barbeta •

Hospital Universitário Antônio Pedro - Av. Marquês do Paraná, 303.

Postal Code: 24033-900, Niterói, RJ – Brazil

E-mail: leticiabarbeta@gmail.com

DOI: 10.5935/abc.20190132

were women: Dr. Bettina Ferro de Souza and Dr. Glaura F. D. Martins (Figure 1). Besides that, due to the high percentage of cardiologists who do not take good care of their own health,

it is necessary to emphasize the importance of physical and mental healthcare in the medical environment and to promote improvements in working conditions.

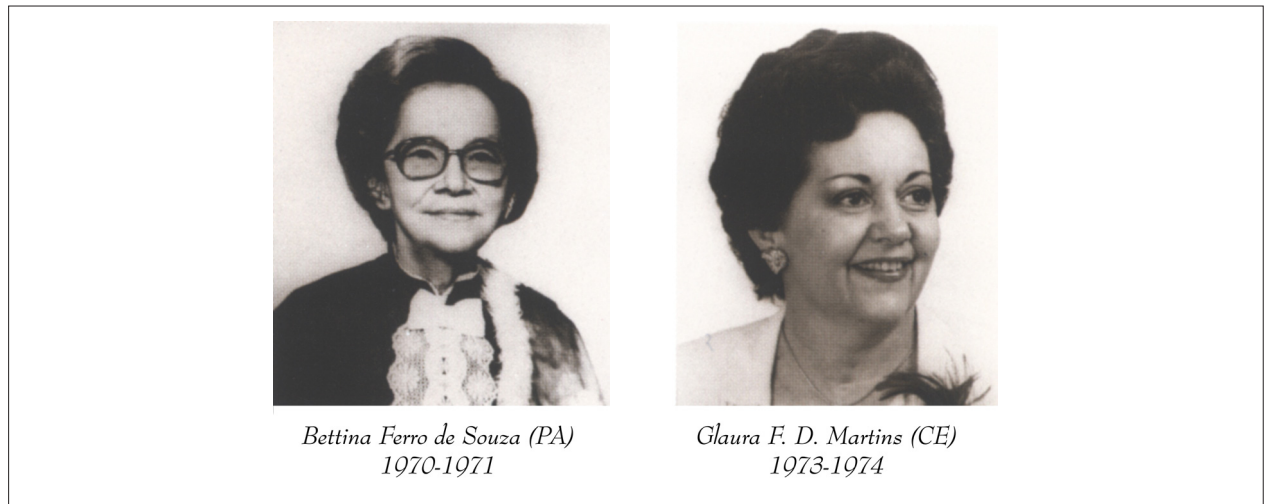


Figure 1 – Former Presidents of SBC. Female medical leaders of cardiology in Brazil.

References

1. Faganello LS, Pimentel M, Polanczyk CA et al. O Perfil do Cardiologista Brasileiro – Uma Amostra de Sócios da Sociedade Brasileira de Cardiologia. *Arq Bras Cardiol.* 2019; 113(1):62-68
2. Scheffer M.(editor) *Demografia Médica no Brasil 2018.* São Paulo,(SP): FMUSP, CFM, Cremesp; 2018. 286 p.
3. Sinclair HC, Joshi A, Allen C, Joseph J, Sohaib SMA, Calver A, et al. Women in Cardiology: The British Junior Cardiologists' Association identifies challenges. *Eur Heart J.* 2019;40(3):227–31.
4. Douglas PS, Rzeszut AK, Bairey Merz CN, Duvernoy CS, Lewis SJ, Walsh MN, et al. Career Preferences and Perceptions of Cardiology Among US Internal Medicine Trainees: Factors Influencing Cardiology Career Choice. *JAMA Cardiol.* 2018 Aug 1;3(8):682–91.



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

Does Mean Platelet Volume Decrease in the presence of Coronary Artery Fistula?

Isa Sincer,¹ Yusuf Çekici,² Mehmet Cosgun,¹ Gulali Aktas,¹ Yilmaz Gunes,¹ Emrah Erdal,¹ Asli Kurtar Mansiroglu,¹ Mehmet Inanir¹

Abant Izzet Baysal University Hospital,¹ Bolu – Turkey

Gaziantep Dr. Ersin Arslan Education and Research Hospital,² Gaziantep – Turkey

Abstract

Background: Coronary artery fistula (CAF) is an abnormal connection that links a coronary artery to a cardiac chamber or another major blood vessel. Several studies have shown the association between mean platelet volume (MPV) and cardiovascular diseases. In the literature, there is no previous study about the association between hematologic parameters and congenital CAF. For this reason, we aimed to investigate the association of MPV with CAF.

Methods: 70 patients with normal coronary arteries and 50 with coronary artery fistulas were included. Routine blood and biochemical parameters were measured before the arteriography. Differences between groups for continuous variables were analyzed with t- test or Mann-Whitney test. P values < 0.05 were considered significant. Regression analysis was used to find independent predictors of CAF.

Results: Baseline patient demographics, including age and clinical risk factors, were similar between the groups. Compared to the control group, median (IQR) High-density lipoprotein cholesterol (HDL) levels were significantly higher ($p=0.04$) and MPV levels were significantly lower in the CAF group (8.84 ± 1.71 fL vs. 10.43 ± 1.34 , $p < 0.001$). In the multivariate analysis, only MPV was a significant predictor of CAF ($p < 0.001$, 95% CI for OR: 0.438 (0.306-0.629). A negative correlation was found between MPV and fistulae in Pearson's correlation test ($r: -0.454$, $p < 0.001$). An MPV level of < 9,6 fL showed sensitivity, specificity, positive predictive value and negative predictive value of 80%, 68%, 71% and 78% respectively (AUC = 0.766, 95% CI, 0.678–0.854) for the prediction of CAF.

Conclusion: The present study suggests that MPV may decrease in patients with CAF. (Arq Bras Cardiol. 2019; 113(1):71-76)

Keywords: Arteriovenous Fistula; Coronary Artery Disease; Mean Platelet Volume; Angiography; Endothelium/dysfunction.

Introduction

Coronary artery fistula (CAF) is an abnormal connection that links a coronary artery to a cardiac chamber or another major blood vessel.¹ In the former case, although CAF is generally congenital, the development and dissemination of interventional and surgical techniques over the years, with a higher prevalence of acquired forms, has led to a change in etiology.² CAF is frequently identified incidentally through diagnostic angiography. Very rarely, ischemia may occur due to increased myocardial oxygen demand, and presents with angina or dyspnea on during exertion. The exact incidence of CAF is not certain, since the underdiagnosis rate is high. However, several studies have reported the presence of CAF in 0.13–0.22% of adults undergoing coronary angiography.³ Around 75% of incidentally-found CAFs are small and

clinically silent. Up to 90% of all CAFs are single and multiple fistulae, present in 10.7–16% of the cases.⁴ Coronary artery fistulae arise more commonly from the right coronary artery (%50–60%) and often drain into the right heart (80%).¹ A fistula between a coronary artery and a right structure shows a continuous flow from coronary vasculature to the low-pressure right chamber. When the drainage site is located in the left atrium or pulmonary vein, there is an effective left-to-left shunt that determines a volume overload to the left heart only. This volume overload may lead to endothelial dysfunction. In the case of a large-caliber CAF, coronary steal may play a role in myocardial ischemia.⁵ Several studies have shown the association between mean platelet volume (MPV) and cardiovascular diseases.^{6,7}

In the literature, there is no previous study about the association between hematological parameters and congenital coronary artery fistulas.

For this reason, we aimed to investigate the association of MPV with CAF.

Methods

Angiographic data of the patients who underwent coronary angiography (CAG) between 2014 February and 2018 March were retrospectively analyzed. A total

Mailing Address: Isa Sincer •

Abant Izzet Baysal University Hospital - Department of Cardiology - Alpagut mah. 223 sok.no:20 Camlibel apt. BOLU, Bolu 14280 – Turkey

E-mail: isasincer@yahoo.com

Manuscript received July 03, 2018, revised manuscript October 05, 2018, accepted November 01, 2018

DOI: 10.5935/abc.20190088

of 120 patients were included: 70 with normal coronary arteries and 50 with CAF with no associated critical coronary artery stenosis. Coronary angiography was performed due to ischemic changes in ECG, positive exercise test or myocardial perfusion scintigraphy for ischemia.

Clinical and laboratory findings were obtained by reviewing the patients' files. Hypertension was defined as blood pressure $> 140/90$ mmHg or receiving antihypertensive medication. Diabetes mellitus was defined as having fasting glucose level > 126 mg/dL or receiving anti-diabetic medication. Presence of total cholesterol > 200 mg/dL or triglycerides > 150 mg/dL was accepted as hyperlipidemia. Patients with a history of acute coronary syndrome in the last 6 months, history of coronary artery stenting or bypass operation, idiopathic dilated or hypertrophic cardiomyopathy, congestive heart failure, moderate to severe renal failure, severe hepatic dysfunction, atrial fibrillation, severe valvular disease, systemic inflammatory diseases (e.g. rheumatoid arthritis, lupus erythematosus), malignancy, history of blood transfusion in the last 3 months, recent infection (1 month), leukemia or thrombocytopenia, were excluded. The local institutional board approved the study.

Peripheral venous blood samples were drawn from patients who were admitted for angiography or during regular follow-up checkups. Serum glucose, creatinine, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol levels were measured using an automatic biochemical analyzer (Architect C8000, USA). Complete blood count and platelet volume were determined using simultaneous optical and impedance measurements (Cell Dyn 3700; Abbott Diagnostics, Lake Forest, Illinois, USA). Platelet, lymphocyte, monocytes, white blood cell (WBC) and MPV values of each patient were recorded.

Coronary angiographies were performed through the radial or femoral artery. The coronary angiographies were evaluated by three interventional cardiologists who were blinded to the clinical and laboratory data of the patients. The fistula location, drainage site, and the fistula shape were evaluated.

Statistical analyses were carried out using the SPSS 18.0 Statistical Package Program for Windows (SPSS Inc., Chicago,

Illinois, USA). The distribution of the variables in the study groups was analyzed by the Kolmogorov-Smirnov test. Normally-distributed variables were compared by *t*-test and expressed as mean $\pm$ standard deviation. Variables without normal distribution were compared with the Mann-Whitney U-test and expressed as median (interquartile range). Qualitative variables were expressed as numbers and percentages. The differences between independent groups were assessed by Student's *t*-test for normally-distributed quantitative variables and Mann-Whitney U-test for variables without normal distribution, whereas Chi-square test was used for qualitative variables. Pearson's correlation test was used to assess the correlations of MVP with CAF presence. The univariate analysis was used to disclose the association of variables with CAF. Thereafter, to determine the independent prognostic factors of CAF, the multivariate logistic regression model with the forward-stepwise method was used with variables that were found to be significant in the univariate analysis. A receiver operating curve (ROC) analysis was performed to find MPV sensitivity and specificity, aiming to predict the presence of coronary fistulae. All results were considered statistically significant at the level of $p < 0.05$.

Results

Baseline patient demographics, including age and clinical risk factors, were similar between the groups, except that the number of females was significantly lower in the fistula group. Previous medications were also comparable between two groups (Table 1). Compared to the control group, HDL-cholesterol levels were significantly higher in the CAF group. However, serum blood glucose, creatinine and other lipid levels were not significantly different (Table 2).

Although the platelet, lymphocyte, monocytes and WBC counts were not significantly different between the two groups, mean MPV levels were significantly lower in the CAF group (8.84 ± 1.71 fL vs. 10.43 ± 1.34 , $p < 0.001$) (Table 2).

In the multivariate logistic analysis, a forward-stepwise model including MPV, platelet, lymphocyte, monocytes, and WBC counts showed that only MPV was a significant predictor of CAF

Table 1 – General characteristics of the study groups

Baseline characteristics	Fistula (n = 50)	Control (n = 70)	p
Age (mean $\pm$ SD) (years)	58 $\pm$ 12	55 $\pm$ 8	0.123 ^a
Male/female	32/18	24/46	0.001 ^b
Hypertension (%)	14 (28%)	13 (19%)	0.223 ^b
Smoking	24 (48%)	35 (50%)	0.829 ^b
Family history	10 (20%)	12 (17%)	0.115 ^b
Diabetes mellitus	12 (24%)	9 (13%)	0.113 ^b
Acetyl salicylic acid	17 (34%)	21 (30%)	0.119 ^b
Statin	15 (30%)	18 (26%)	0.143 ^b
ACE inhibitor	2 (4%)	3 (4%)	0.938 ^b
B-blocker	17 (34%)	20 (29%)	0.26 ^b

ACE: angiotensin-converting enzyme; SD: Standard deviation, data were compared with Student's *t*-test (^a) and Chi-square test (^b).

Table 2 – Laboratory data of the study cohort

	Fistula (n = 50)	Control (n = 70)	p
Creatinine(mg/dL)	0.80 (0.30)	0.80 (0.22)	0.50 ^a
Fasting plasma glucose (mg/dL)	98 (57)	101(17)	0.90 ^a
LDL-cholesterol (mg/dL)	111 (48)	101(56)	0.47 ^a
HDL-cholesterol (mg/dL)	42 (16)	44(24)	0.04 ^a
Triglycerides (mg/dL)	150 (115)	157(107)	0.49 ^a
Total cholesterol (mg/dL)	190 (54)	187(54)	0.56 ^a
Hematocrit (%)	42 (7)	41(6)	0.45 ^a
Monocytes (x10 ³ µL)	0.61(0.36)	0.62(0.24)	0.42 ^a
Hemoglobin (gr/dL)	13.9 ± 1.8	13.3 ± 1.9	0.12 ^b
MPV(fL)	8.84 ± 1.71	10.43 ± 1.34	< 0.001 ^b
Platelet count (k/mm ³)	271 ± 82.72	268 ± 78	0.85 ^b
Lymphocytes (x10 ³ µL)	2.37 ± 0.751	2.46 ± 1.01	0.60 ^b
WBC (x10 ³ µL)	8.2 ± 3.1	6.35 ± 2.01	0.18 ^b

^a Data without normal distribution shown as median (interquartile range), a comparison with Mann Whitney U test, ^b comparison with t-test. MPV: mean platelet volume; WBC: White blood cells; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol.

($p < 0.001$, 95% CI for OR: 0.438 (0.306–0.629). A significant negative correlation was found between MPV and fistulae in Pearson's correlation test ($r: -0.454$, $p < 0.001$). An MPV level < 9.6 fL had a sensitivity, specificity, positive predictive value and negative predictive value of 80%, 68%, 71% and 78% respectively (AUC = 0.766, 95% CI, 0.678–0.854) for CAF prediction. The overall accuracy of MPV when determining the presence of CAF was 75% (Figure 1).

The right ventricular diameter was slightly increased in the CAF group. Other echocardiographic measurements were similar (Table 3). The angiographic features of the fistula group are summarized in Table 4.

Discussion

In this study, we showed that MPV levels were significantly reduced in the CAF group when compared to that with normal coronary arteries. Coronary arterial fistulas are usually asymptomatic. Usual symptoms include dyspnea, angina or fatigue on exertion and, occasionally, arrhythmias. Congestive heart failure may occasionally occur in childhood.^{8–11} In adults, myocardial ischemia may occur due to coronary steal.¹²

In our study, the right ventricular end-diastolic diameters of the fistula group were statistically larger than those in the control group regarding echocardiographic findings. The pathophysiological changes in CAF depend on the pressure difference between the fistula origin and its location and size.¹ This pressure difference determines the length, the width and tortuosity of the fistula.¹ A left-to-right shunt is found in over 90% of the cases.¹ When the fistula drains to the right side of the heart, there is a continuous flow from the fistula due to presence of low pressures in the right chambers, the volume load is increased to the right heart and, consequently, to the pulmonary vascular bed, the left

heart chambers. However, when the fistula drains into the left heart chambers, pulmonary blood flow does not increase. Therefore, similar to our findings, right heart chamber dilation is more frequent than left-heart dilation. Especially in the case of a large-caliber CAF, the shifting of blood away from the normal coronary circulation may result in the coronary steal phenomenon and, consequently, in ischemia.¹

Automatic blood count analyzers calculate MPV in routine assays. It is affected by inflammation and it is accepted as a marker of thrombocyte activation.¹³ A number of diseases, such as metabolic syndrome, myocardial infarction, acute ischemic stroke and diabetes mellitus have been associated with increased MPV.^{13,14} Conversely, lower MPV has been reported in subjects with rheumatoid arthritis, Nasal Polyps and ankylosing spondylitis.^{15,16} Similarly, several studies in the literature reported decreased levels of MPV in irritable bowel disease.^{17,18} It has been proposed that lower and higher MPV values in different conditions are related with high and low-grade inflammation states. Gasparyan et al.¹⁹ reported that diseases characterized by marked inflammation (e.g. rheumatoid arthritis) are associated with lower MPV values, while low-grade inflammation (e.g. nasal polyps, Behcet's disease) are associated with increased MPV levels.¹⁹

MPV was found to be higher in most cardiovascular diseases.^{13,14} However, interestingly, MPV in CAF patients was found to be lower than in the control groups. Therefore, we speculate that, unlike acute coronary syndromes, CAF may be associated with a low but continuous inflammatory burden. Unfortunately, this is the first study in the literature that evaluated MPV in CAF. Another author suggested that activated platelets tend to enlarge and cause an elevation in MPV value, and might be utilized in such active inflammatory process, leaving smaller platelets, thus causing a reduction in MPV.²⁰ On the other hand, other authors speculate that overproduction of pro-inflammatory cytokines and acute

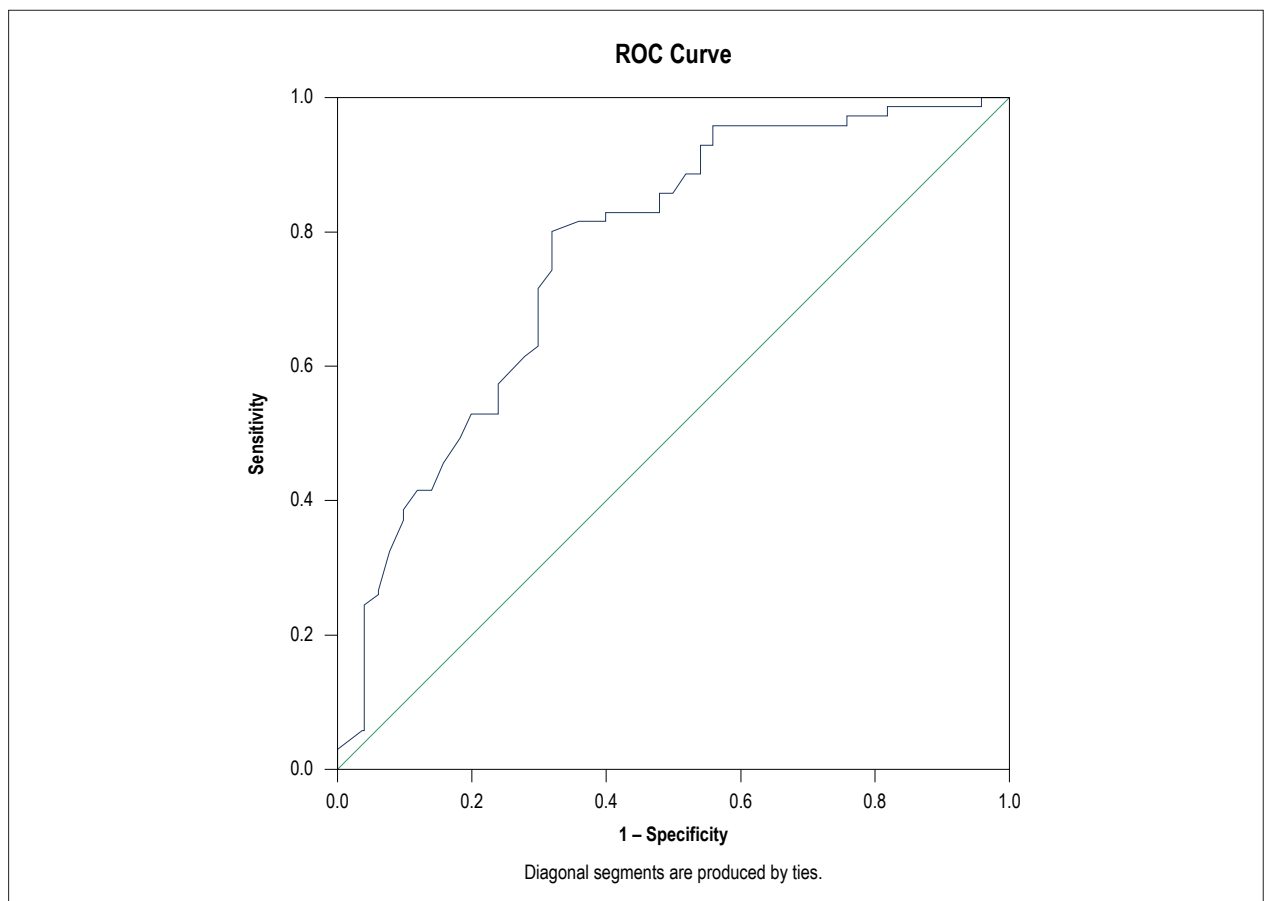


Figure 1 – Diagonal segments are produced by ties.

Table 3 – Echocardiographic findings of the study population

Variables	Fistula	Control	p
Left ventricle end-diastolic diameter(cm)	4.7 ± 0.65	4.6 ± 0.53	0.22
Left ventricle end-systolic diameter(cm)	3.4 ± 0.86	3.3 ± 0.72	0.123
Ejection Fraction (%)	61.4 ± 8.9	63.1 ± 0.76	0.11
Right ventricle end-diastolic diameter(cm)	2.87 ± 0.81	2.46 ± 0.4	0.04
Left atrium diameter(cm)	3.3 ± 0.64	3.4 ± 0.71	0.19

phase reactants can suppress the dimensions of platelets by interfering with the process of megakaryopoiesis in the bone marrow.¹³ HDL-cholesterol was found to have a modulating effect on endothelial dysfunction through antioxidant and anti-inflammatory effects.²¹ Reduced HDL-cholesterol levels in CAF subjects, when compared to controls, may be the underlying cause of endothelial dysfunction in CAF, but prospective studies are still needed to confirm that.

The retrospective cross-sectional design and single-center nature are two important limitations of the present report. Another limitation could be the relatively small study cohort. As far as we know, there are no data about the association of inflammation and CAF. The lack of analysis of inflammatory

markers is another important limitation. However, to the best of knowledge, this is the first study that reported an association between CAF and MPV.

Conclusion

The present study suggests that lower MPV may be associated with CAF. Although an elevated MPV is well established in conditions with higher cardiovascular mortality, this is the first time lower MPV was found in a cardiac disease with low mortality. Therefore, we suggest the use of MPV to determine CAF in patients, considering it is a cost-effective and simple test.

Table 4 – Angiographic findings of the fistula

Variables	N (%)
Origin of fistulae	
RCA	16(32%)
ADA	15(30%)
CX	15(30%)
LMCA	4(8%)
Drainage site of the fistulae	
Pulmonary artery	15(30%)
Right ventricle	17(34%)
Right atrium	5(10%)
Left ventricle	13(26%)
Shape of the fistulae	
Straight	4(8%)
Single tortuous	21(42%)
Multiple tortuous	25(50%)

RCA: right coronary artery; ADA: anterior descending artery; CX: circumflex artery; LMCA: main coronary artery.

Author contributions

Conception and design of the research: Sincer I, Cosgun M, Gunes Y, Mansiroglu AK, Inanir M; Acquisition of

data: Sincer I, Çekici Y, Cosgun M, Erdal E, Mansiroglu AK, Inanir M; Analysis and interpretation of the data: Sincer I, Çekici Y, Aktas G, Gunes Y; Statistical analysis: Sincer I, Cosgun M, Aktas G, Erdal E; Writing of the manuscript: Aktas G, Gunes Y, Erdal E, Mansiroglu AK, Inanir M; Critical revision of the manuscript for intellectual content: Sincer I, Çekici Y, Aktas G, Gunes Y.

Potential Conflict of Interest

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

Sources of Funding

There were no external funding sources for this study.

Study Association

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

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Nome da Instituição under the protocol number 68246970/903-99. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013.

References

- Buccheri D, Chirco PR, Geraci S, Caramanno G, Cortese B. Coronary artery fistulae: anatomy, diagnosis and management strategies. *Heart Lung Circ*. 2018; 27 (8):940-51.
- Said SA, el Gamal MI, van der Werf T. Coronary arteriovenous fistulas: collective review and management of six new cases--changing etiology, presentation, and treatment strategy. *Clin Cardiol*. 1997; 20 (9):748-52.
- Latson LA. Coronary artery fistulas: how to manage them. *Cathet Cardiovasc Interv*. 2007; 70 (1):110-16.
- Challoumas D, Pericleous A, Dimitrakaki IA, Danelatos C, Dimitrakakis G. Coronary arteriovenous fistulae: a review. *Int J Angiol*. 2014; 23 (1):1-10.
- Gowda RM, Vasavada BC, Khan IA. Coronary artery fistulas: clinical and therapeutic considerations. *Int J Cardiol*. 2006; 107 (1):7-10.
- Tsiara S, Elisaf M, Jagroop IA, Mikhailidis DP. Platelets as predictors of vascular risk: is there a practical index of platelet activity? *Clin Appl Thromb Hemost*. 2003; 9 (3):177-90.
- Ege MR, Acikgoz S, Zorlu A, Sincer I, Guray Y, Guray U, et al. Mean platelet volume: an important predictor of coronary collateral development. *Platelets*. 2013;24(3):200-4.
- Wilde P, Watt I. Congenital coronary artery fistulae: six new cases with a collective review. *Clin Radiol*. 1980; 31(3):301-11.
- McNamara JJ, Gross RE. Congenital coronary artery fistula. *Surgery*. 1969; 65 (1):59-69.
- Alkhulaifi AM, Horner SM, Pugsley WB, Swanton RH. Coronary artery fistulas presenting with bacterial endocarditis. *Ann Thorac Surg*. 1995; 60(1):202-4.
- Skimming JW, Walls JT. Congenital coronary artery fistula suggesting a "steal phenomenon" in a neonate. *Pediatr Cardiol*. 1993;14(3):174-5.
- Qureshi SA. Coronary arterial fistulas. *Orphanet J Rare Dis*. 2006; 1(1):51
- Bath PM, Butterworth RJ. Platelet size: measurement, physiology and vascular disease. *Blood Coagul Fibrinolysis*. 1996;7(2):157-61.
- Dastjerdi MS, Emami T, Najafian A, Amini M. Mean platelet volume measurement, EDTA or citrate? *Hematology*. 2006;11(5):317-9.
- Kisacik B, Tufan A, Kalyoncu U, Karadag O, Akdogan A, Ozturk MA, et al. Mean platelet volume (MPV) as an inflammatory marker in ankylosing spondylitis and rheumatoid arthritis. *Joint Bone Spine*. 2008;75(3):291-4.
- Aktas G, Sit M, Tekce H, Alcelik A, Savli H, Simsek T, et al. Mean platelet volume in nasal polyps. *The West Indian Med J*. 2013; 62(6):515-8.
- Kapsoritakis AN, Koukourakis MI, Sfiridaki A, Potamianos SP, Kosmadaki MG, Koutroubakis IE, et al. Mean platelet volume: a useful marker of inflammatory bowel disease activity. *Am J Gastroenterol*. 2001; 96(3):776-81.
- Jaremo P, Sandberg-Gertzen H. Platelet density and size in inflammatory bowel disease. *Thromb Haemost*. 1996;75(4):560-1.
- Gasparyan AY, Ayyazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: a link between thrombosis and inflammation? *Curr Pharm Des*. 2011;17(1):47-58.
- Polinska B, Matowicka-Karna J, Kemona H. Assessment of the influence of the inflammatory process on the activation of blood platelets and morphological parameters in patients with ulcerative colitis (colitis ulcerosa). *Folia Histochem Cytol*. 2011;49(1):119-24.
- Natarajan P, Ray KK, Cannon CP. High-density lipoprotein and coronary heart disease: current and future therapies. *J Am Coll Cardiol*. 2010;55(13):1283-99.



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

GLA Gene Mutation in Hypertrophic Cardiomyopathy with a New Variant Description: Is it Fabry's Disease?

Ândrea Virgínia Chaves-Markman,^{1,2,3,4,5} Manuel Markman,² Eveline Barros Calado,¹ Ricardo Flores Pires,⁶ Marcelo Antônio Oliveira Santos-Veloso,^{3,4,5} Catarina Maria Fonseca Pereira,⁷ Andréa Bezerra de Melo da Silveira Lordsleem,^{1,3,5} Sandro Gonçalves de Lima,^{1,3,5} Brivaldo Markman Filho,¹ Dinaldo Cavalcanti de Oliveira^{1,4,5}

Universidade Federal de Pernambuco - Hospital das Clínicas - Área Acadêmica de Medicina Clínica - Centro de Medicina Clínica - CCM,¹ Recife, PE - Brazil

Hospital Agamenon Magalhães,² Recife, PE - Brazil

Universidade Federal de Pernambuco - Grupo de pesquisa em Epidemiologia e Cardiologia (EPICARDIO),³ Recife, PE - Brazil

Pós Graduação em Inovação Terapêutica (PPGIT) - Universidade Federal de Pernambuco,⁴ Recife, PE - Brazil

Centro Universitário Maurício de Nassau - Curso de Medicina,⁵ Recife, PE - Brazil

Clínica de Doenças Metabólicas,⁶ Porto Alegre, RS - Brazil

Cetogene AG,⁷ Rostock - Germany

Abstract

Background: Fabry disease (FD) is an X-linked lysosomal storage disorder caused by mutations in the alpha galactosidase A gene (GLA) that lead to the enzymatic deficiency of alpha galactosidase (α -Gal A), resulting in the accumulation of globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3), causing multiple organ dysfunctions.

Objective: To perform GLA gene screening in a group of patients with echocardiographic diagnosis of hypertrophic cardiomyopathy (HCM).

Methods: A cross-sectional study was conducted with HCM patients from a university hospital. Patients with coronary artery disease and valvulopathies were excluded. Mutation analysis of the GLA gene was performed. In male subjects, the analysis was performed after evidence of low α -Gal A activity.

Results: 60 patients with echocardiographic diagnosis of HCM were included. Age ranged from 12 to 85 years and 60% were women. Mean myocardial fibrosis percentage on MRI was $10.7 \pm 13.1\%$ and mean ventricular thickness was 18.7 ± 6.7 mm. Four patients had the following GLA gene mutations: c.967C>A (p.Pro323Thr), not yet described in the literature; c.937G>T (p.Asp313Tyr); and c.352C>T (p.Arg118Cys). All patients had normal levels of lyso-Gb3 and non-ischemic myocardial fibrosis on magnetic resonance imaging; one patient had proteinuria and one patient had ventricular tachycardia.

Conclusion: In this study, the frequency of mutation in the GLA gene in patients with HCM was 6.7%. A novel mutation in exon 6 of the GLA gene, c.967C>A (p.Pro323Thr), was identified. Patients with HCM may have GLA mutations and FD should be ruled out. Plasma (lyso-Gb3) levels do not seem to be sufficient to attain a diagnosis and organ biopsy should be considered. (Arq Bras Cardiol. 2019; 113(1):77-84)

Keywords: Fabry Disease/genetic; Cardiomyopathy, Hypertrophic; Hypertrophy, Left Ventricular; Glycosphingolipids.

Introduction

Hypertrophic cardiomyopathy (HCM) is the most prevalent cardiopathy of genetic origin, caused by >1400 mutations in genes encoding proteins that are components of cardiac sarcomeres and other proteins of related structures, such as Z-discs and intercalated discs.¹⁻³ Due to advances in molecular biology techniques, the differential diagnosis of HCM has

been extended, and other genetic disorders that present with ventricular hypertrophy have been reported.⁴

Fabry disease (FD) is a rare X-linked genetic condition. It is caused by inborn errors in glycosphingolipid metabolism due to mutations in the gene encoding the enzyme α -galactosidase A (α -Gal A). Total or partial deficiency of this enzyme results in progressive accumulation of globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3) in some tissues, particularly in the blood vessels, kidneys, and myocardium.⁵⁻⁷ More than 900 mutations with different effects on α -Gal A enzyme activity have been described.^{8,9}

The incidence of FD is estimated at 1:40,000 to 1:17,000 individuals, and both male homozygous and female heterozygous may be affected.^{5,6,8,9} Two phenotypes are recognized: a classic form that is characterized by an early-onset with manifestations during childhood, and a late-onset form that frequently affects only one organ.^{5,6,8} Cardiac changes

Mailing Address: Ândrea Virgínia Chaves-Markman •

Rua Doutor Pedro de Melo Cahú, 51/2102. Postal Code 51020-080, Boa Viagem, Recife, PE - Brazil

E-mail: andreachaves.cardio@gmail.com

Manuscript received June 14, 2018, revised manuscript October 31, 2018, accepted November 01, 2018

DOI: 10.5935/abc.20190112

seem to be present in the early stages of life; however, it is usually not clinically detectable until the third or fourth decade of life. Deposits of glycosphingolipids in valves and coronary vessels are frequent, which may cause complete atrioventricular block, mitral insufficiency, left ventricular hypertrophy (LVH), or myocardial ischemia.¹⁰

Currently, specific mutations are associated with the cardiac variant showing myocardial hypertrophy that is clinically similar to HCM.^{11,12} Patients with FD are at risk for developing cerebrovascular disease (CVD), cardiac sudden death, and renal failure, and these patients can benefit from specific treatments.^{13–15}

In this study, a screening for the *GLA* gene was performed in a group of patients with echocardiographic diagnosis of hypertrophic cardiomyopathy (HCM).

Methods

Subjects

A cross-sectional study was conducted in a convenience sample of patients with HCM treated at the cardiology outpatient clinic at a university hospital in Recife, Pernambuco, Brazil. All patients with an echocardiographic diagnosis of HCM based on the European Society of Cardiology¹⁶ criteria were included. Patients with coronary artery disease, valvulopathies and hypertensive cardiomyopathy were excluded.

Definitions of HCM

A Transthoracic Echocardiography (TTE) was used to establish the diagnosis of HCM based on the following criteria: unexplained maximum ventricular thickness (MVT) ≥ 15 mm in any cardiac segment or a MVT ≥ 13 mm in a patient with family history of HCM. The obstructive presentation was defined by a left ventricular outflow gradient ≥ 30 mmHg at rest or after Valsalva maneuver or in orthostatism.^{13,16}

Echocardiographic assessment

The TTE was previously performed in all subjects to establish the diagnosis of HCM (Vivid 7 or Vivid E9 GE) with offline dataset analysis (EchoPac®, GE Healthcare, Little Chalfont, United Kingdom). The diameters of the interventricular septum and the left ventricular (LV) posterior wall, LV end diastolic volume, and LV end systolic volume were determined through M-mode or 2D imaging. The MVT of all segments were measured in the parasternal short axis. The ejection fraction (EF) and diastolic function were calculated using Simpson's method and pulsatile Doppler, respectively.^{17,18}

Magnetic resonance imaging

Magnetic resonance imaging (MRI) was performed in all patients with *GLA* mutation to assess the presence of myocardial fibrosis using the delayed myocardial enhancement technique (DMET). A 1.5-T MRI scanner (MAGNETOM Essenza, Siemens Healthcare, Erlangen, Germany) with an eight-channel phased

array coil was used. The images were acquired in the cardiac short axis, from the base to the apex, with 8-mm slices and 2-mm intervals using the T1-weighted echo-gradient sequence. An inversion recovery prepulse and adjusted inversion time were used to neutralize the myocardial signal. Image acquisition was started at approximately 8–10 min after the infusion of gadolinium contrast at a dosage of 0.2 mmol/kg. DMET increases the amount of contrast between the normal tissue (dark due to signal neutralization) and the fibrotic tissue (white due to enhancement of gadolinium in the T1-weighted sequence).¹⁹

Electrocardiography and Dynamic electrocardiography (24-h Holter)

A resting 12-lead electrocardiogram was performed in all patients. A continuum digital recorder (*Cardio Light*®, Cardio Sistemas Comercial Industrial, São Paulo, Brazil) was used to record and analyze the Holter tests for 24 h. The electrodes were positioned in the electrocardiographic derivations MV1, MV4, and MV6. The results were analyzed using the *Cardiomanager* 540® (Cardio Sistemas Comercial Industrial, São Paulo, Brazil) software by an independent observer searching for cardiac arrhythmias.

Molecular and enzymatic essays

All included patients underwent digit blood capillary puncture and blood samples were collected on filter paper. The samples were dried for 3–4h at room temperature, stored in a plastic envelop at 4°C, and sent to the Centogene Laboratory (Rostock, Germany):

Molecular analysis to determine *GLA* gene mutations was performed in the samples from the female subjects, whereas mutation analysis was performed after evidence of low α -Gal A activity in male subjects. The expression level and enzymatic activity of the biomarker lyso-Gb3 were identified through high-performance liquid chromatography and tandem mass spectrometry.

The *GLA* gene was analyzed using polymerase chain reaction (PCR) and sequencing of all coding regions and highly conserved exon–intron boundaries through next-generation sequencing with Illumina HiSeq (Illumina, California, USA). *GLA* gene analysis was performed in all patients with HCM.

Statistical analyses

Data were analyzed descriptively using the Statistical Package for the Social Sciences version 20.0 (IBM Company, Armonk, NY, USA). Before analyzing the continuous variables, the data sets were tested for normality by performing the Shapiro-Wilk test. Normally-distributed continuous variables were presented with measures of central tendency and dispersion (mean and standard deviation), and categorical variables were described as absolute (n) and relative (%) frequencies. Comparative analysis was performed using Pearson's chi-square test for categorical variables. Numerical variables were analyzed using the paired Student's *t*-test. The significance level was defined as 5% throughout the entire statistical analysis ($p < 0.05$).

Paired student's *t*-test was used to compare the baseline characteristics of both HCM and *GLA* mutation groups, and Pearson's chi-square test was used to identify any associations between the clinical variables.

Ethical standards

The study was approved by the Institutional Ethics Committee and was carried out according to Resolution 196/96 of the Brazilian National Health Council, which deals with the guidelines and standards for research involving human subjects. The investigation was also conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients before inclusion in this study.

Results

We included 60 patients with an echocardiographic diagnosis of HCM that underwent molecular tests for FD. Their age ranged from 12 to 85 years (mean 42.3 ± 17), and 60% ($n = 36$) were women. Four patients, three of which were women, had *GLA* gene mutations, corresponding to 6.7% of our sample.

Syncope and dyspnea were the most frequent cardiac symptoms in all patients. Asymmetric septal hypertrophic

cardiomyopathy was the most frequent type in patients without *GLA* mutations (61.5%) and in the *GLA* mutation group (50%). EF was similar in both groups. The most common electrocardiographic patterns of all patients were left ventricular hypertrophy (37.9%), atrioventricular block (13.8%) and left bundle branch block (10.3%). The clinical and epidemiological baseline characteristics of our sample are shown in Table 1.

Three mutations with heterozygote variants were found: c.967C>A (p.Pro323Thr), which is a novel mutation not yet described in literature (Figure 1); c.937G>T (p.Asp313Tyr); and c.352C>T (p.Arg118Cys). One homozygous variant was also found: c.352C>T (p.Arg118Cys). Five male patients underwent molecular analysis due to low α -Gal A enzyme activity; however, none of them had *GLA* gene mutations. The clinical and epidemiological characteristics of the patients with *GLA* gene mutations are described in Table 2.

Discussion

In our sample of 60 patients with HCM, we determined through molecular tests that the prevalence of *GLA* mutation was 6.7%. Additionally, we found a new mutation in the *GLA* gene. Enzyme replacement was started in one patient with *GLA* mutation.

Table 1 – Clinical characteristics and complementary test results of patients

		HCM (n=56)	GLA mutation (n = 4)	p-value
Age (years)		42.3 $\pm$ 17.0	58.5 $\pm$ 15.2	0.11
Gender (female)		59.9%	75%	0.53
EF (%) †		67.6 $\pm$ 8.6	65.0 $\pm$ 4.2	0.43
Cardiac symptoms	Dyspnea	8%	25%	0.80
	Precordial pain	5%	-	
	Syncope	17.5%	50%	
	Palpitation	5%	-	
	Dizziness	7%	-	
Predominance of LVH †	Apical	5.56%	25%	0.38
	Concentric	25%	25%	
	AS	61.1%	50%	
	AM	0.05%	-	
	PMH	2.78%	-	
MVT (mm) †		19.1 $\pm$ 6.4	18.7 $\pm$ 0.9	0.98
Fibrosis on MRI (%)		11.0 $\pm$ 13.9	12.0 $\pm$ 11.6	0.82
ECG alteration	LVO	38.5%	100%	0.83
	LAE	10.3%	-	
	AVR	28.6%	-	
	LBBB	10.3%	25%	
	AVB	5.1%	50%	
	QRSFrag	20.5%	-	

HCM: hypertrophic cardiomyopathy; EF: ejection fraction; LVH: left ventricular hypertrophy; AS: Asymmetric septal; AM: anteromedial; PMH: papillary muscle hypertrophy; MVT: maximum ventricular thickness; MRI: magnet resonance imaging; ECG: electrocardiogram; LVO: left ventricular outflow tract; LAE: left atrium enlargement; AVR: abnormal ventricular repolarization; LBBB: left bundle branch block; AVB: atrioventricular block; QRSFrag: QRS fragmentation. † measurement via transthoracic echocardiography (TTE).

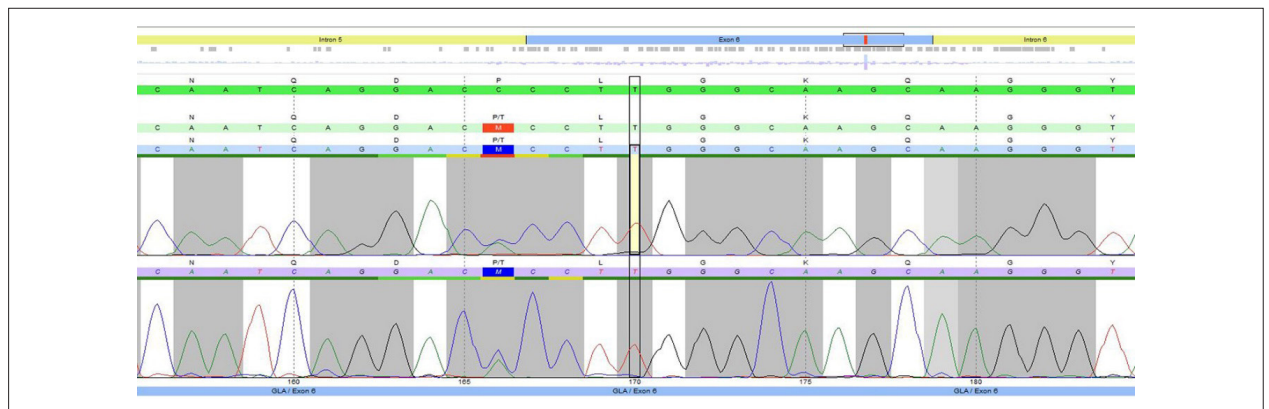


Figure 1 – Chromatogram of the novel GLA gene mutation: c.967C>A (p.Pro323Thr).

Table 2 – Clinical characteristics and complementary test results of FD patients

	Patient 1	Patient 2	Patient 3	Patient 4
Age (years)	69	39	72	53
Gender	F	F	F	M
Cardiac symptoms	Syncope	Syncope, dyspnea	No	No
Extracardiac symptoms	TIA	Acroparesthesia, intolerance to heat/cold, mood changes	Acroparesthesia, arteria thrombosis	ICVA
ECG	RHR, LVO, FDAVB, LBBB	RHR, LVO	RHR, LVO, FDAVB	RHR, LVO
24h Holter	8 episodes of VT, 677 PVC	No arrhythmias	Paroxysmal AFib	No arrhythmias
EF †	67%	60%	70%	65%
Predominance of LVH †	Apical	Asymmetrical septal hypertrophy	Asymmetrical septal hypertrophy	Concentric
MVT (mm) †	19	20	18	18
Diastolic dysfunction †	Mild	Pseudonormal	Mild	Mild
LVOTO †	No	No	No	No
Fibrosis on MRI	6%	28%	13%	1.36%
FSD	Yes	Yes	No	No
ICD	Yes	Yes	No	No
GLA gene mutation	c.967C>A (p. Pro323Thr)	c.937G>T (p.Asp313Tyr)	c.352C>T (p.Arg118Cys)	c.352C>T (p.Arg118Cys)
High lyso-Gb3	No	No	No	No
Low α-Gal A	NM	NM	NM	Yes
Proteinuria	No	No	Yes	No

F: female; M: male; TIA: transitory ischemic attack; ICVA: ischemic cerebrovascular accident; ECG: electrocardiogram; RHR: regular heart rate; LVO: left ventricular overload; FDAVB: first degree atrio-ventricular block; LBBB: left bundle branch block; VT: ventricular tachycardia; PVC: premature ventricular contraction; AFib: atrial fibrillation; EF: ejection fraction; LVH: left ventricular hypertrophy; MVT: maximum ventricular thickness; LVOTO: left ventricular outflow tract obstruction; MRI: magnetic resonance imaging; FSD: family sudden death; ICD: implantable cardioverter defibrillator; NM: not measured. † measurement via transthoracic echocardiography (TTE).

FD has X-linked inheritance. The classic X-linked disorder generally shows a vertical transmission, in which heterozygous females transmit the allele down to their offspring. The majority of mutations in X-linked genes result in diseases that will only occur in males. However, some of the X-linked diseases show different rates of penetrance and expressivity in both genders. In FD, heterozygous individuals (females) are usually affected, but tend to have a milder and more variable phenotype than homozygous ones (males).²⁰

The prevalence of FD is estimated to be 0.02–0.09:10,000 in the overall population, though molecular screening in newborns suggests a higher prevalence.^{21,22} Regarding the cardiac variant, the prevalence may be as high as 12%, depending on the method used.^{23–26}

The mean maximum ventricular thickness (MVT) in patients with GLA mutation in our sample was greater than that in previous studies. The mean MVT was 11.6 ± 3.3 mm in the study by Koskenvuo et al.,²⁷ and only eight patients

had LVH. The mean MVT was 16.7 ± 1.9 mm in the study by Takenaka et al.,²⁸ which is closer to that shown in this study. Patients with GLA mutation were screened from an HCM sample, which may explain the tendency for the higher mean values of MVT.

In our study, patients with GLA mutations had an older mean age. This finding could perhaps be attributed to the fact that the cardiac variant of FD has a later onset.

Regarding the hypertrophy pattern, FD is predominantly associated with concentric hypertrophy.²⁹ However, some studies found a higher prevalence of the asymmetrical variety,²⁵ which was in accordance with our results. This variety is usually associated with severe presentations of the disease.^{25,29}

Atrioventricular block was present in the electrocardiographic (ECG) findings in two patients with GLA mutation (50%), which is in accordance with the findings from previous studies.²⁹ However, repolarization abnormalities were common in patients with HCM, but not in patients with FD, as expected. These abnormalities are associated with mild concentric hypertrophy.³⁰ In our study, only one patient showed concentric hypertrophy, which may explain the absence of repolarization abnormalities in the ECG results of our patients with GLA mutation.

The mean myocardial fibrosis percentage on MRI was $12 \pm 11.6\%$ and $10.5 \pm 13.7\%$ in patients with GLA mutation and no mutation, respectively. However, there was no statistically significant differences between the compared groups ($p = 0.85$). Although the clinical presentation of FD has been well described, the physiopathological mechanism linking the intracellular accumulation of Gb3 to tissue damage and clinical manifestations is still not well established.³¹ It is hypothesized that intracellular storage of Gb3 triggers important physiopathological cascades related to inflammatory processes, leading to myocardial cell changes and, over time, to fibrosis.³¹⁻³³

GLA mutation was not associated with any specific late gadolinium enhancement (LGE) pattern on MRI. Patient 2 shows LGE in the basal midventricular septum, anterior septum, lateral inferior and apical segments of the left ventricle. Patient 3 shows LGE in the interventricular septum, inferior wall and in the right ventricle insertions. Patient 4 shows LGE in the basal segments of the inferior septum and inferior wall segments of the right ventricle. Information about LGE in patient 1 was not available.

One of the variants found has not been described in previous studies and in the *Exome Aggregation Consortium*, *Exome Sequencing Project* or *1000 Genomes Browser* databases. The variant, c.967C>A (p.Pro323Thr), is located in exon 6 of the GLA gene. This mutation results in the substitution of a threonine amino acid by a proline amino acid at position 323 of the protein. This position shows a highly conserved nucleotide and a highly conserved amino acid, with moderated physico-chemical differences between the proline and threonine amino acids. It has characteristics of pathogenicity based on the analysis using *Polyphen-2*, *SIFT*, *MutationTaster*, and *Align-GVGD* software. Patient 1, the carrier of this mutation, had severe cardiac defects, manifested as arrhythmia and hypertrophy, with no other explainable causes.

The variant 352C>T (p.Arg118Cys) in exon 2 of the GLA gene was initially described to be pathogenic by Spada et al.³⁴ According to Ferreira et al.,³⁵ the moderated enzymatic deficiency related to p.Arg118Cys may not be sufficient to cause major complications of FD, suggesting low pathogenicity.³⁵ This mutation was found in two unrelated patients (patients 3 and 4), both with LVH. Patient 3 also showed first-degree atrioventricular block and paroxysmal atrial fibrillation on ECG, as well as proteinuria. Patient 4 had a history of ischemic stroke. Despite the controversy over the pathogenicity of this variant, the authors believe it may cause specific organ manifestations, such as cardiac and cerebral involvement.

With regard to the third variant found in exon 6 of the GLA gene, GLA c.937G>T (p.Asp313Tyr) in patient 2, there are also contradictory results about its pathogenicity. Some studies showed that genotype D313Y is not responsible for severe organic lesions similar to those associated with the well-established genotypes of classic FD.³⁶

Lenders et al.³⁶ and Niemann et al.,³⁷ reported that the presence of this variant is potentially associated with important white matter lesions in the central nervous system.^{36,37} The patient had severe cardiac hypertrophy, a history of uncontrolled systemic arterial hypertension, and complained of generalized pain with emotional lability. She has been receiving enzymatic replacement therapy for six months and has shown significant improvement of symptoms and blood pressure control.

The study of variants c.937G>T (p.Asp313Tyr) and c.352C>T (p.Arg118Cys) show contradictory results in the literature, but the authors believe they are pathogenic. The variant p.Asp313Tyr, found in this group, was identified in members of the same family and all follow the X-linked inheritance, with important cardiac hypertrophy and symptoms. Regarding the p.Arg118Cys, which has also shown controversial results in the literature, it was found in two patients from different families in this group. One is a homozygous male with cardiac hypertrophy and ischemic stroke; the other one is a heterozygous female patient also with cardiac hypertrophy, arterial thrombosis and proteinuria. The authors are currently working with the objective of gathering more evidence about the pathogenicity of these variants in the other family members. The new variant found, c.967C>A (p.Pro323Thr) seems to be pathogenic according to the analysis carried out with *Polyphen-2*, *SIFT*, *MutationTaster* and *Align-GVGD* software. As stated before, the patient is a heterozygous female with cardiac hypertrophy and transitory ischemic attack and investigation of the family members suggest pathogenicity.

Although the 352C>T (p.Arg118Cys) and c.937G>T (p.Asp313Tyr) variants are controversial as to pathogenicity, the families' heredogram confirms an X-linked inheritance. One of the most relevant results of the study was the identification of a new mutation in the GLA gene that seems to be pathogenic, in addition to the identification of 14 other carriers among the relatives of the four index patients. The probability of performing enzyme replacement therapy and pharmacological chaperones emphasizes the importance of an early diagnosis of FD³⁸⁻⁴⁰ and the search to identify the pathogenicity of the variants found.

Limitations

The main limitations of our study were: the absence of sample calculation, the small sample size due to the disease rarity and the small number of patients with *GLA* mutations (statistical analyses were limited). Also, molecular analysis of sarcomeric genes in patients with HCM was not performed.

T1 mapping was performed on MRI images only for patient 4. At the time of the other scans, MRI T1 mapping was not available at our institution.

The authors understand that a renal or cardiac biopsy could be performed to confirm pathogenicity for those uncertain variants.

Conclusion

In this study, the frequency of mutations in the *GLA* gene in patients with hypertrophic cardiomyopathy was 6.7%. A novel mutation in exon 6 of the *GLA* gene, c.967C>A (p.Pro323Thr), was identified. Patients with HCM may have *GLA* mutations and Fabry disease should be ruled out. Plasma lyso-GB3 levels do not seem to be sufficient to attain a diagnosis, and organ biopsy should be considered.

Author contributions

Conception and design of the research: Chaves-Markman AV, Markman Filho B, Oliveira DC; Acquisition of data: Chaves-Markman AV, Markman M, Calado EB, Pereira CME, Lordsleem, ABMS; Analysis and interpretation of the data:

Chaves-Markman AV, Santos-Veloso MAO, Lima SG, Markman Filho B, Oliveira DC; Statistical analysis: Lima SG, Oliveira DC; Writing of the manuscript: Chaves-Markman AV, Calado EB, Pires RF; Critical revision of the manuscript for intellectual content: Chaves-Markman AV, Markman Filho B, Oliveira DC.

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 Ândrea Virgínia Chaves-Markman from Universidade Federal de Pernambuco.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Centro de Pesquisa Aggeu Magalhães under the protocol number 3076174. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Baptista A, Magalhães P, Leão S, Carvalho S, Mateus P, Moreira I. Screening for fabry disease in left ventricular hypertrophy: documentation of a novel mutation. *Arq Bras Cardiol*. 2015;105(2):139-44.
2. Boggio P, Luna PC, Abad ME, Larralde M. Doença de Fabry. *An Bras Dermatol*. 2009;84(4):367-76.
3. Niemann M, Weidemann F. Echocardiography in Fabry disease. *Cardiogenetics*. 2013;3(1):e3.
4. Mattos BP, Torres MAR, Freitas VC. Diagnostic evaluation of hipertrophic cardiomyopathy in its clinical and preclinical phases. *Arq Bras Cardiol*. 2008;91(1):55-62.
5. Albuquerque CV. Anderson Fabry's disease: cardiac manifestations. *Rev Bras Ecocardiogr Imagem Cardiovasc*. 2012;25(3):214-8.
6. Gómez MG, Varas C, Morales M, Bonacic F, Alvarez M, Rojas A. Cardiac involvement in patients with Fabry's disease. *Rev Chil Cardiol*. 2013;32(1):28-33.
7. Kaminsky P, Noel E, Jaussaud R, Leguy-Seguín V, Hachulla E, Zenone T, et al. Multidimensional analysis of clinical symptoms in patients with Fabry's disease. *Int J Clin Pract*. 2013;67(2):120-7.
8. Hughes DA. Fabry disease: will markers of early disease enable early treatment and better outcomes? *Curr Opin Cardiol*. 2016;31(4):434-9.
9. Stenson PD, Mort M, Ball E V, Evans K, Hayden M, Heywood S, et al. The Human Gene Mutation Database: towards a comprehensive repository of inherited mutation data for medical research, genetic diagnosis and next-generation sequencing studies. *Hum Genet*. 2017;136(6):665-77.
10. Linhart A, Elliott PM. The heart in Anderson-Fabry disease and other lysosomal storage disorders. *Heart*. 2007;93(4):528-35.
11. Csányi B, Hategan L, Nagy V, Obál I, Varga ET, Borbás J, et al. Identification of a novel *GLA* gene mutation, p.Ile239Met, in Fabry Disease with a predominant cardiac phenotype. *Int Heart J*. 2017;58(3):454-8.
12. Hsu TR, Hung SC, Chang FP, Yu WC, Sung SH, Hsu CL, et al. Later onset Fabry disease, cardiac damage progress in silence. *J Am Coll Cardiol*. 2016;68(23):2554-63.
13. Banikazemi M, Bultas J, Waldek S, Wilcox WR, Whitley CB, McDonald M, et al. Agalsidase-beta therapy for advanced Fabry disease: a randomized trial. *Ann Intern Med*. 2007;146(2):77-86.
14. Germain DP, Charrow J, Desnick RJ, Guffon N, Kempf J, Lachmann RH, et al. Ten-year outcome of enzyme replacement therapy with agalsidase beta in patients with Fabry disease. *J Med Genet*. 2015;52(5):353-8.
15. Wu JC, Ho CY, Skali H, Abichandani R, Wilcox WR, Banikazemi M, et al. Cardiovascular manifestations of Fabry disease: relationships between left ventricular hypertrophy, disease severity, and alpha-galactosidase A activity. *Eur Heart J*. 2010;31(9):1088-97.
16. Task Force members, Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35(39):2733-79.
17. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29(4):277-314.

18. Steeds RP, Garbi M, Cardim N, Kasprzak JD, Sade E, Nihoyannopoulos P, et al. EACVI appropriateness criteria for the use of transthoracic echocardiography in adults: a report of literature and current practice review. *Eur Heart J Cardiovasc Imaging*. 2017;18(11):1191-204.
19. Sara L, Szarf G, Tachibana A, Shiozaki AA, Villa AV, Oliveira AC, et al. II Diretriz de Ressonância Magnética e Tomografia Computadorizada Cardiovascular da Sociedade Brasileira de Cardiologia e do Colégio Brasileiro de Radiologia. *Arq Bras Cardiol*. 2014;103(6 supl 3):1-86.
20. Pinto LL, Vieira TA, Giugliani R, Schwartz IV. Expression of the disease on female carriers of X-linked lysosomal disorders: a brief review. *Orphanet J Rare Dis*. 2010 May 28;5:14.
21. Mechtler TP, Stary S, Metz TF, De Jesús VR, Greber-Platzer S, Pollak A, et al. Neonatal screening for lysosomal storage disorders: feasibility and incidence from a nationwide study in Austria. *Lancet*. 2012;379(9813):335-41.
22. Hwu WL, Chien YH, Lee NC, Chiang SC, Dobrovolny R, Huang AC, et al. Newborn screening for Fabry disease in Taiwan reveals a high incidence of the later-onset GLA mutation c.936+919G>A (IVS4+919G>A). *Hum Mutat*. 2009;30(10):1397-405.
23. Hagege AA, Caudron E, Damy T, Roudaut R, Millaire A, Etchecopar-Chevreuil C, et al. Screening patients with hypertrophic cardiomyopathy for Fabry disease using a filter-paper test: the FOCUS study. *Heart*. 2011;97(2):131-6.
24. Monserrat L, Gimeno-Blanes JR, Marín F, Hermida-Prieto M, García-Honrubia A, Pérez I, et al. Prevalence of Fabry disease in a cohort of 508 unrelated patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2007;50(25):2399-403.
25. Chimenti C, Pieroni M, Morgante E, Antuzzi D, Russo A, Russo MA, et al. Prevalence of Fabry disease in female patients with late-onset hypertrophic cardiomyopathy. *Circulation*. 2004;110(9):1047-53.
26. Sachdev B, Takenaka T, Teraguchi H, Tei C, Lee P, McKenna WJ, et al. Prevalence of Anderson-Fabry disease in male patients with late onset hypertrophic cardiomyopathy. *Circulation*. 2002;105(12):1407-11.
27. Koskenvuo JW, Engblom E, Kantola IM, Hartiala JJ, Saraste A, Kiviniemi TO, et al. Echocardiography in Fabry disease: diagnostic value of endocardial border binary appearance. *Clin Physiol Funct Imaging*. 2009;29(3):177-80.
28. Takenaka T, Teraguchi H, Yoshida A, Taguchi S, Ninomiya K, Umekita Y, et al. Terminal stage cardiac findings in patients with cardiac Fabry disease: An electrocardiographic, echocardiographic, and autopsy study. *J Cardiol*. 2008;51(1):50-9.
29. Yousef Z, Elliott PM, Cecchi F, Escoubet B, Linhart A, Monserrat L, et al. Left ventricular hypertrophy in Fabry disease: a practical approach to diagnosis. *Eur Heart J*. 2013;34(11):802-8.
30. Goldman ME, Cantor R, Schwartz MF, Baker M, Desnick RJ. Echocardiographic abnormalities and disease severity in Fabry's disease. *J Am Coll Cardiol*. 1986;7(5):1157-61.
31. De Francesco PN, Mucci JM, Ceci R, Fossati CA, Rozenfeld PA. Fabry disease peripheral blood immune cells release inflammatory cytokines: role of globotriaosylceramide. *Mol Genet Metab*. 2013;109(1):93-9.
32. Seydelmann N, Wanner C, Störk S, Ertl G, Weidemann F. Fabry disease and the heart. *Best Pract Res Clin Endocrinol Metab*. 2015;29(2):195-204.
33. Biancini GB, Vanzin CS, Rodrigues DB, Deon M, Ribas GS, Barschak AG, et al. Globotriaosylceramide is correlated with oxidative stress and inflammation in Fabry patients treated with enzyme replacement therapy. *Biochim Biophys Acta*. 2012;1822(2):226-32.
34. Spada M, Pagliardini S, Yasuda M, Tükel T, Thiagarajan G, Sakuraba H, et al. High incidence of later-onset Fabry disease revealed by newborn screening. *Am J Hum Genet*. 2006;79(1):31-40.
35. Ferreira S, Ortiz A, Germain DP, Viana-Baptista M, Caldeira-Gomes A, Camprecios M, et al. The alpha-galactosidase A p.Arg118Cys variant does not cause a Fabry disease phenotype: data from individual patients and family studies. *Mol Genet Metab*. 2015;114(2):248-58.
36. Lenders M, Duning T, Schelleckes M, Schmitz B, Stander S, Rolfs A, et al. Multifocal white matter lesions associated with the D313Y mutation of the α -Galactosidase A gene. *PLoS One*. 2013;8(2):e55565.
37. Niemann M, Rolfs A, Giese A, Mascher H, Breunig F, Ertl G, et al. Lyso-Gb3 indicates that the Alpha-Galactosidase A Mutation D313Y is not clinically relevant for Fabry disease. *JIMD Rep*. 2013;7:99-102.
38. Kampmann C, Perrin A, Beck M. Effectiveness of agalsidase alfa enzyme replacement in Fabry disease: cardiac outcomes after 10 years' treatment. *Orphanet J Rare Dis*. 2015 Sep 29;10:125.
39. Biegstraaten M, Arngrímsson R, Barbey F, Boks L, Cecchi F, Deegan PB, et al. Recommendations for initiation and cessation of enzyme replacement therapy in patients with Fabry disease: the European Fabry Working Group consensus document. *Orphanet J Rare Dis*. 2015 Mar 27;10:36.
40. Germain DP, Hughes DA, Nicholls K, Bichet DG, Giugliani R, Wilcox WR, et al. Treatment of Fabry's disease with the Pharmacologic Chaperone Migalastat. *N Engl J Med*. 2016;375(6):545-55.



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

Description of a New GLA Gene Variant in a Patient with Hypertrophic Cardiomyopathy. Is it Fabry Disease?

Marcelo Imbroinise Bittencourt¹⁰

Hospital Universitário Pedro Ernesto da Universidade do Estado do Rio de Janeiro, Rio de Janeiro, RJ – Brazil

Short editorial related to the article: *GLA Gene Mutation in Hypertrophic Cardiomyopathy with a New Variant Description: Is it Fabry's Disease?*

Hypertrophic cardiomyopathy (HCM) is the most common monogenic cardiovascular disease in Brazil, with a prevalence of approximately 1:500 individuals. The autosomal dominant inheritance pattern is the most common one. More than 20 genes have been reported as being associated with the disease, and most of them encode sarcomeric proteins.^{1,2}

Fabry disease (FD) is a lysosomal storage disorder caused by α -galactosidase-A deficiency due to a mutation in the *GLA* gene, with X-linked inheritance. It causes alterations in multiple organs, including the heart, mimicking HCM.³

In a publication by Favalli et al.,⁴ a prospective 10-year FD screening study, hypertrophy with wall thickness >13 mm was the most common finding of the disease, occurring in approximately 50% of individuals with mutations in the *GLA* gene, followed by acroparesthesia and renal failure.⁴

A better understanding of the disease prevalence has been attained as its screening has been carried out in several populations. A Chinese study published in the past decade indicates a prevalence of 1:1600 men.⁵ Some mutations can cause the disease with limited heart manifestations, and this has already been reported in previous studies.^{6,7} The hypertrophy pattern may be useful to differentiate FD from HCM, but it is not an easy task. In HCM, the distribution of the left ventricular hypertrophy is characteristically asymmetric and heterogeneous, with several possible phenotypes. In FD, the hypertrophy is typically concentric, without obstruction of the left ventricular outflow tract, and the tapering of the basal portion of the left ventricular posterior wall is a characteristic of the final stage of the disease.

In the current issue of the Brazilian Archives of Cardiology, Chaves-Markman et al.⁸ found mutations in the *GLA* gene in

6.7% of a cohort of 60 HCM patients and reported a new variant, c.967C>A (p.Pro323Thr), a missense mutation. This mutation has not been previously described, showing the originality of this work.⁸ Two other variants were described in this group of patients: c.937G>T (p.Asp313Tyr) and c.352C>T (p.Arg118Cys). Interestingly, three of the four patients who had mutations in the *GLA* gene were females, a phenomenon also found in the article published by Csányi B et al.,⁷ when they described the Ile239Met variant.⁷ This finding is little expected in patients with FD due to inactivation of the X chromosome in heterozygous women, resulting in milder symptoms.⁹

The main question of this article to be discussed is whether the new mutation is in fact responsible for the left ventricular hypertrophy. The detection of any rare missense variant represents a challenge for the conclusion of causality in any genetic condition, and FD is no different. Therefore, since only the analysis of the *GLA* gene was performed, one cannot rule out the possibility that another pathogenic variant in some other gene that causes HCM may be present in the patient in which the c.967C>A (p.Pro323Thr) variant was detected, as it was correctly highlighted in the study limitations.

Nevertheless, it is a very relevant finding, as the genetic alteration is in a highly conserved area of the protein and this has an impact on the definition of pathogenicity of a new variant. It should be emphasized that the patient had a transient ischemic attack among the extracardiac symptoms, without any documentation of atrial fibrillation, which could be associated with FD.

As emphasized by the author, the histopathological study is important for the diagnosis of FD, and it may help the groups that are discovering new variants of uncertain significance in the *GLA* gene to define its actual importance, especially in patients with the isolated cardiac form.

Every diagnostic method has its limitations, and the identification of a complex condition such as FD will increasingly require a multiple approach by integrating several modalities (genetics, biochemistry, imaging and histology), which will generate more evidence for each experiment. Definitely, the study carried out by Chaves-Markman et al. represents an important step in the genetic screening and knowledge acquisition of the association between HCM and FD in the Brazilian population.

Keywords

Alpha-Galactosidase/deficiency; Fabry Disease/genetics; Fabry Disease/metabolismo; cardiomyopathy, Hypertrophic; Multiple Chronic Conditions.

Mailing Address: Marcelo Imbroinise Bittencourt •

Rua Dona Maria, 71 BL 1 Apto 902. Postal Code 20541-030, Vila Isabel, Rio de Janeiro, RJ – Brazil

E-mail: mib@cardiol.br, marceloibittencourt@gmail.com

DOI: 10.5935/abc.20190126

References

1. Task Force Members, Elliott PM, Anastakis A, Borger MA, Borggrefe M, Cecchi F, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: The Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J*. 2014;35(39):2733-79.
2. Bittencourt MI, Mourilhe-Rocha R, Abanesi Filho FM. Hypertrophic cardiomyopathy. *Rev Bras Cardiol*. 2010;23(1):17-24.
3. Monserrat L, Gimeno-Blanes JR, Marin F, Hermida-Prieto M, García-Honrubia A, Pérez I, et al. Prevalence of Fabry disease in a cohort of 508 unrelated patients with hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2007;50(25):2399-403.
4. Favalli V, Disabella E, Molinaro M, Tagliani M, Scarabotto A, Serio A, et al. Genetic screening of Anderson-Fabry disease in probands referred from multispecialty clinics. *J Am Coll Cardiol*. 2016;68(10):1037-50.
5. Lin HY, Chong KW, Hsu JH, Yu HC, Shih CC, Huang CH, et al. High incidence of the cardiac variant of Fabry disease revealed by newborn screening in the Taiwan Chinese population. *Circ Cardiovasc Genet*. 2009;2(5):450-6.
6. Nakao S, Takenaka T, Maeda M, Kodama C, Tanaka A, Tahara M, et al. An atypical variant of Fabry's disease in men with left ventricular hypertrophy. *N Engl J Med*. 1995;333(5):288-93.
7. Csányi B, Hategan L, Nagy V, Obál I, Varga ET, Borbás J, et al. Identification of a Novel GLA Gene Mutation, p.Ile239Met, in Fabry Disease with a predominant cardiac phenotype. *Int Heart J*. 2017;58(3):454-8.
8. Chaves-Markman AV, Markman M, Calado EB, Pires RF, Santos-Veloso MAO, Pereira CMF, et al. GLA gene mutation in hypertrophic cardiomyopathy with a new variant description: Is it Fabry's disease? *Arq Bras Cardiol*. 2019;113(1):77-84.
9. Mehta A, Hughes DA. Fabry Disease: Synonyms: Anderson-Fabry disease, alpha galactosidase A deficiency. In: Pagon RA, Adam MP, Ardinger HH, et al. eds. *GeneReviews®* [Internet]. Seattle, WA: University of Washington, Seattle; 1993-2017. [Cited in 2002 Aug 2]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK1292/>.



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

Applicability of the Electro-Vectorcardiogram in Current Clinical Practice

Carlos Alberto Pastore,¹⁰ Nelson Samesima, Horacio Gomes Pereira Filho, Nancy Maria Martins de Oliveira Tobias, Bruna Affonso Madaloso, Mirella Esmanhotto Facin

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

Abstract

The electrocardiogram (ECG) has been reinvigorated by the identification of electrical alterations that were not definitely clarified before. In this context, and mainly regarding the definition of arrhythmogenic substrates, the association of the ECG with the vectorcardiogram (VCG) has gathered much more information about the cardiac electrical phenomena, thus allowing us to differentiate potentially fatal cases from benign ones. Obtaining a VCG concomitantly with the performance of an ECG has led to a significant gain in the definition of extremely sophisticated pathologies, which function suffer some type of structural or dynamic alterations, involving either the reduction or enhancement of ionic channels and currents.

The classic aspects of the ECG/VCG association in the differential diagnosis of myocardial infarctions, conduction disorders, atrial and ventricular hypertrophies, and the correlations between these electrical disorders are still valid and assertive. The association of these pathologies is further clarified when they are seen through the ECG/VCG dyad.

The three-dimensional spatial orientation of both the atrial and the ventricular activity provides a far more complete observation tool than the ECG linear form. The modern analysis of the ECG and its respective VCG, simultaneously obtained by the recent technique called electro-vectorcardiogram (ECG/VCG), brought a significant gain for the differential diagnosis of some pathologies. Therefore, we illustrate how this type of analysis can elucidate some of the most important diagnoses found in our daily clinical practice as cardiologists.

Introduction

The study of vectorcardiography began during the 1940's and publications reached a peak between the 1960's and 1970's, correlating this method with the heart diseases best known at that time. The great difficulty then was linked to the fact that the VCG device could not be easily moved around. The images were thus not immediately obtained, and so the

vectorcardiogram was a tool to be used *a posteriori* to resolve doubts about specific electrocardiograms in some special situations. Additionally, the advent of echocardiography and its later improvement, as well as the emergence of computed tomography and magnetic resonance imaging, led to a decreased use of both the electrocardiogram and, mainly, of the vectorcardiogram from the 1980's until the end of the 1990's. This temporal gap, associated to a diminished interest in electrovectorcardiography, resulted in a significant decrease in the number of cardiology centers capable of performing and interpreting a vectorcardiogram.

However, with the development of invasive electrophysiology (electroanatomic mapping), genetics and molecular biology, many electrical conditions have been unveiled, resulting in the identification of their clinical/electrocardiographic patterns, since such conditions can lead to sudden death.¹⁻⁷

The technological developments seen during the 1990s also affected electrovectorcardiography. The sophistication brought by the use of computers, algorithmic systems and Fourier transforms allowed us to obtain vectorcardiographic information in a much simpler and quicker form, in color, and as three-dimensional images.

The electrocardiogram (ECG) was therefore reinvigorated by the identification of electrical alterations that had not yet been definitely observed, so that from the year 2000 until the present decade an increasing number of publications related to electrovectorcardiography has been observed. In this context, and mainly regarding the definition of arrhythmogenic substrates, it was observed that the association of the ECG and the vectorcardiogram (VCG) methods could provide much more information about the cardiac electrical phenomena, thus increasing its employment and allowing us to differentiate potentially fatal cases from benign ones.⁸⁻¹⁰

We now find ourselves in a moment where the performance and reading of the vectorcardiogram is carried out in just a few specific centers around the world. Moreover, our team is involved with the teaching of electrocardiography to undergraduate and postgraduate students in the medical area. Therefore, we feel there is an urgent need to teach vectorcardiography, considering that its spatial visualization of the cardiac electrical activation makes it a lot easier to understand and memorize the basic and more complex electrocardiographic notions.¹¹

Obtaining a VCG concomitantly with the performance of an ECG has led to a significant gain in the definition of extremely sophisticated pathologies, of which genetic mutations cause their function to suffer some type of structural or dynamic alterations, involving either the reduction or enhancement of ionic channels and currents.

Keywords

Electrocardiography/methods; Vectocardiography/methods; Electrophysiological Phenomena; Internal Medicine/methods

Mailing Address: Carlos Alberto Pastore •

Av. Dr. Eneas de Carvalho Aguiar, 44 AB. Postal Code 05403-000, Cerqueira Cesar, São Paulo, SP – Brazil

E-mail: ecg_pastore@incor.usp.br

Manuscript received September 19, 2018, revised manuscript January 10, 2019, accepted February 13, 2019

DOI: 10.5935/abc.20190095

The classic aspects of the ECG/VCG association in the differential diagnosis of myocardial infarctions, conduction disorders, atrial and ventricular hypertrophies, and the correlations between these electrical disorders are still valid and assertive.^{12,13} The association of these pathologies is further clarified when they are seen through the ECG/VCG dyad. (Figure 1)

Based on the abovementioned facts, during the last decade we were able to develop the performance of the binomial electrovectorcardiogram in the context of the most varied pathologies. This binomial can add sophistication to the already known clinical entities, in addition to a greater accuracy of the recent electrocardiographic definitions (such as Brugada, early repolarization, etc.)

Our experience, both academic and scientific, led us to join these new ECG/VCG acquisitions, and to open a window into the observation of the electrical phenomena of the heart. The literature has shown that the more sophisticated vectorcardiogram makes it easier for us to observe punctual phenomena that are not defined by the ECG.

Limitations

Because there are only a few centers that are capable of performing routine vectorcardiography, there remains no doubt that this comparative study requires specific training, just like any other diagnostic method, through didactic bibliography and distance learning material. The purpose of this publication is guided by the acknowledgement of this situation.

The electrovectorcardiography binomial

The experience with the VCG during these last decades shows the greater specificity and sensitivity of this method to detect the subtleties of these diagnoses. In comparison with the ECG, the VCG shows some advantages; however, when

in association, they can help us differentiate between some very ordinary situations in clinical practice.

The three-dimensional spatial orientation of both the atrial and the ventricular activity provides a far more complete observation tool than the linear form of the ECG. The modern analysis of the ECG and its respective VCG, simultaneously obtained by the recent technique called electro-vectorcardiogram (ECG/VCG), brought a significant gain for the differential diagnosis of some pathologies.^{1,3,4,8,14,15} (Figure 2)

The electro-vectorcardiographic analysis is very rich and consistent for the diagnosis of myocardial infarctions (MI), since the difficulties in defining pathological Q waves or the loss of R waves in the ECG can be very clearly visualized in the ECG/VCG. This association helps us to define the real changes in the direction and orientation of the vectorcardiographic loops created by the areas of myocardial infarction, in both the transverse and the frontal planes.¹⁶⁻¹⁸ (Figure 3)

Another important differential aspect obtained by the electro-vectorcardiogram is the investigation of the presence of a myocardial infarction area in the inferior wall, of a left superior fascicular block, or the association of both pathologies. The association of MIs with the presence of fascicular or troncular blocks can be fully characterized by the ECG/VCG association. The inferior MIs with a left anterosuperior fascicular block (LASFB), and the anterior MIs with a right bundle-branch block (RBBB) are typical examples of the importance of the ECG/VCG association for a differential diagnosis.^{19,20} (Figures 3A and 4A and B)

The spatial orientation of the fascicular blocks can be better understood through the electro-vectorcardiogram. The septal vector orientation and the direction of the vectorcardiographic loop activation neatly characterize the fascicular blocks and their associations through the ECG/VCG, since they define the electrical path of this phenomenon, thus characterizing exactly the position of the blocks.²¹⁻²⁴ (Figures 4A and 5(A and B)

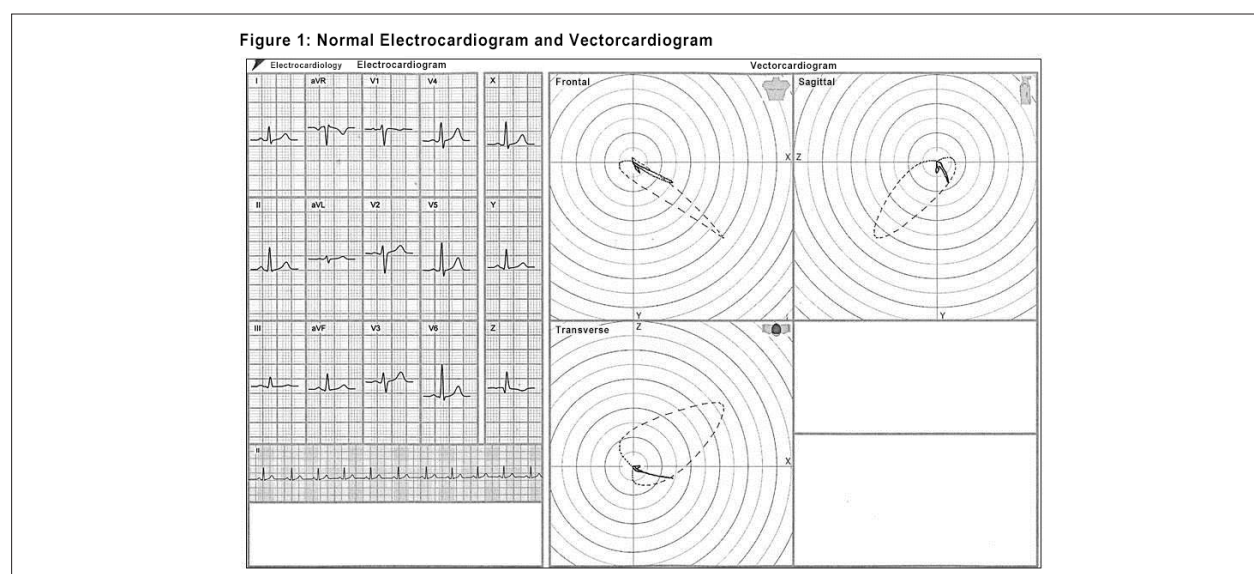


Figure 1 – Electrocardiogram vs. Vectorcardiogram.

Figure 2: Orthogonal planes

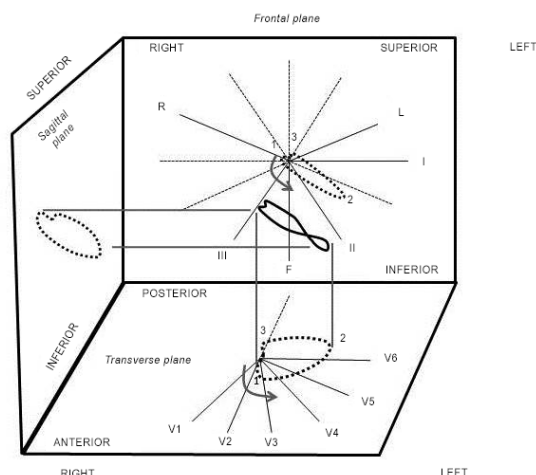


Figure 2 – Electrical activation of the heart and its projection in the three spatial planes, thus giving origin to the vectorcardiographic loops in the respective planes.

The VCG complements the ECG in the analysis of acute myocardial infarctions and makes the differential diagnosis of the associations with blocks and chamber hypertrophies. There is no doubt that the most ordinary situations in the cardiological routine, such as absent or exaggerated R waves from V1 to V3, require a more sophisticated definition in this region that depicts many expressions of different pathologies. Therefore, in this region the ECG/VCG is capable of characterizing the presence of:²²⁻²⁷ (Figures 5B, 6[A, B, C and D])

- a) Left anteromedial fascicular block (LMFB)
- b) Right ventricular hypertrophy (RVH)
- c) Lateral infarction
- d) Ventricular pre-excitation syndrome (WPW)
- e) Brugada syndrome

The ECG/VCG is the gold standard to identify complete and fascicular blocks, because it can differentiate them either in isolation or in association with other blocks. The electrical path marked by the ventricular activation loops can identify the blocks, as well as other associations.^{21,23,28} (Figure 7)

The end-conduction delays, previously denominated incomplete right bundle-branch blocks, are neatly defined by the ECG/VCG. These findings can be mistaken for the left phenomena and also can mimic a myocardial infarction area. Thus, the association of ECG/VCG solves the doubts that arise from the presence of these delays, which can be either the variants from the normal, or even suggest a conduction disorder in specific areas of the right ventricle.

The presence of the end-conduction delay (ECD) is clarified in the ECG/VCG by the $S_1S_2S_3$ pattern, with the S wave in D_2 greater than the one in D_3 , qR in aVR and presence of S wave from V₁ to V₆. The ECG/VCG confirms the ECD position backwardly and to the right in the transverse plane, and upwardly and to the right in the frontal plane.²⁵ (Figure 8)

One of the definitive identifications obtained by the ECG/VCG association is that of the presence of a ventricular pre-excitation (WPW). The presence of the delta wave is very clearly seen in the beginning of the QRS loop by the proximity of the comets at the onset of the QRS loop, characterizing the delay caused by the accessory pathway, thus also establishing the position of the anomalous bundle at the valvular annulus.²⁶ (Figure 9 [A and B])

One of the most recent diagnostic achievements of the ECG/VCG refers to the criteria to establish Brugada syndrome patterns, as well as the early repolarization (ER) phenomenon. It is important to emphasize that, in typical cases, there are no difficulties to make the electro-vectorcardiographic identification of both conditions. Due to the severity of the first, to the variability of the second between normal cases and other pathologies, and also to the possibility of having an early repolarization pattern located in a more anterior area, it became essential to make an adequate distinction between them. From the ECG/VCG viewpoint, there are no guidelines set to date to identify J-wave abnormalities. Specific ECG/VCG patterns of the J-wave abnormalities, namely the Brugada syndrome (BrS), and the early repolarization pattern (RP) were studied by our research team. An important qualitative and quantitative analysis of the ECG/VCG was carried out in all the study population, specifically regarding aspects of the area comprising the terminal portion of the QRS loop, the J point and the ST segment. This analysis showed a neat end-conduction delay (ECD) in all the individuals (in both the BrS and the RP groups). This ECD is characterized by a conduction delay greater than 10 ms at the final portion of the QRS in all the planes, either to the right or to the left (slowing of the comets, which tend to get closer and, eventually, to merge).

Figure 3A: Old inferior myocardial infarction (MI)

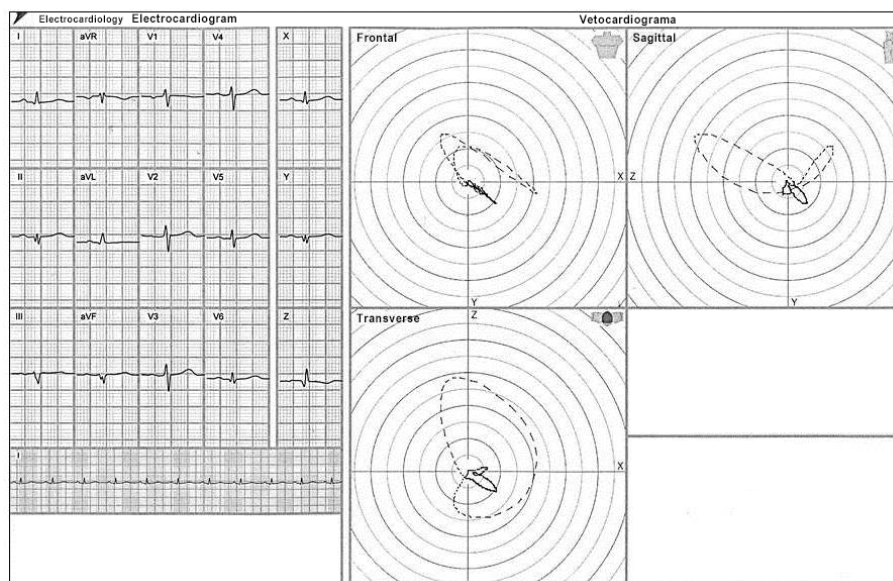


Figure 3B: Old anteroseptal MI

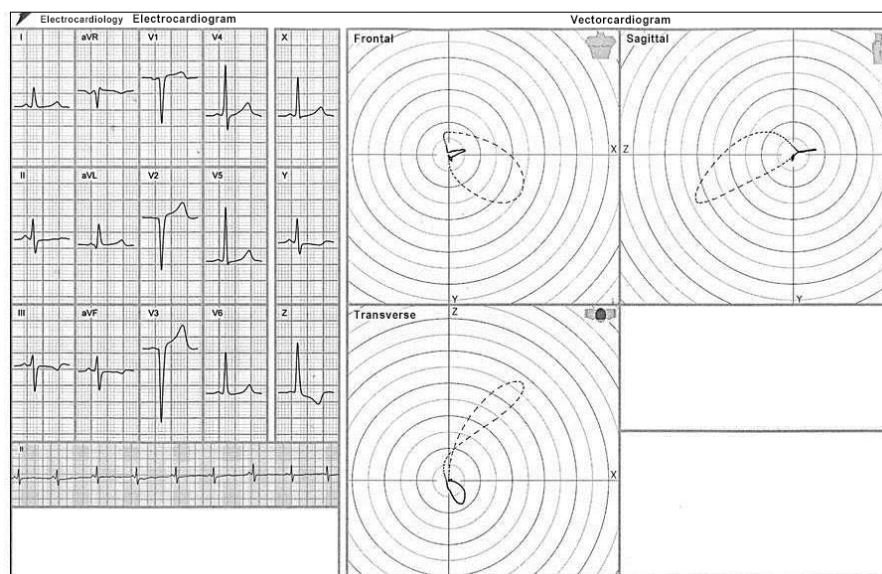


Figure 3 – (A) Presence of myocardial infarction area in the inferior wall, with QRS vectorcardiographic loop onset oriented upwardly and to the left. (B) Aspect of a large myocardial infarction area from V1 to V6 and its respective loop in the transverse plane, with anomalous activation of the septum and exaggerated backward rotation, followed by deformation of the QRS loop.

In the transverse plane, the QRS loops showed a counterclockwise rotation, with the ECD beginning posteriorly and ending anteriorly, with the main difference between the groups being the ECD position.

In BrS type 1 patients (Figure 6D) we see a counterclockwise rotation of the terminal QRS segment, J point and onset of the ST segment around the medial portion, resembling a “nose” in profile. The ECD position was in the right quadrant in all BrS patients and its duration was significantly longer.

A greater than or equal to 30 ms ECD had 100% sensitivity and 77% specificity to diagnose Brugada syndrome. The BrS group showed a break at the end of the QRS loop right after the ECD, which resembled a “nose”, right before the onset of the T-wave loop. This “nose” pattern was present in all the BrS type 1 patients.

In the ER pattern^{9,25} (Figure 10) we see a clockwise rotation (terminal portion of the QRS) of the same segments, resembling a “fishhook”. In all the ER cases the ECD position

Figure 4A: LASFB

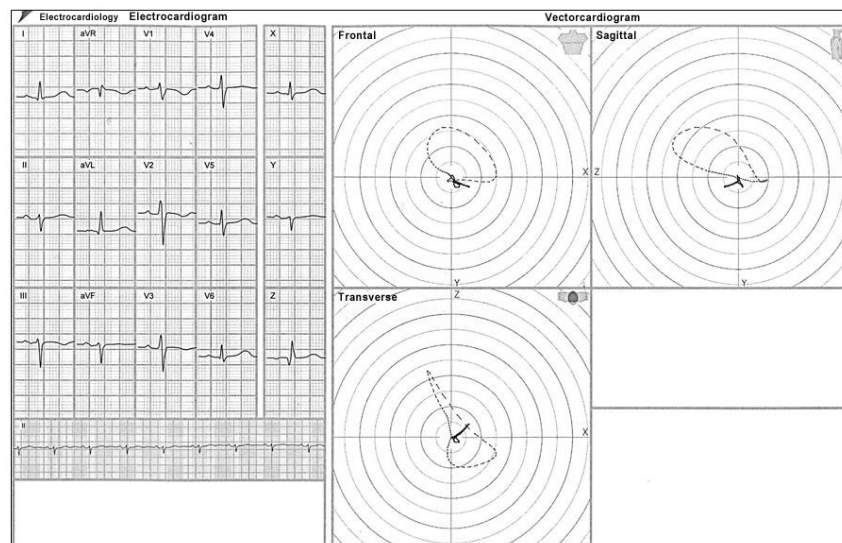


Figure 4B: Old inferior MI + LASFB

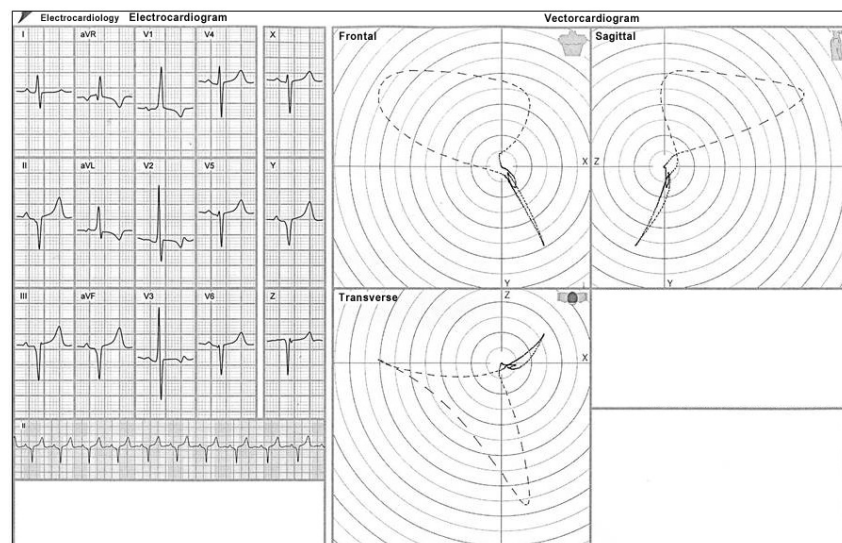


Figure 4 – Aspects of the VCG loops in the Inferior MI (in Fig. 3A of the previous item, note the QRS loop onset upwardly in the frontal plane, with more than 30 ms duration [15 comets]); in Figure 4A – LASFB, observe the QRS loop onset downwardly (through the posterior-inferior division), with counterclockwise rotation and the major portion of the loop oriented upwardly and to the left; and in Figure 4B - LASFB + inferior MI, the association of the two entities; note that the QRS loop in the frontal plane is directed upwardly, with clockwise rotation, and after 30 ms it changes its orientation, with counterclockwise rotation characterizing the LASFB.

was in the left quadrant, with a shorter duration. In 100% of the ER patients, the final portion of the QRS loop showed a fishhook pattern.

Characteristic electro-vectorcardiographic aspects of the type 1 Brugada syndrome (see Figure 6D): transverse plane: QRS loop onset with counterclockwise rotation; ECD began posteriorly and ended anteriorly and in the right quadrant in all BrS patients; BrS showed a “break” at the end of the QRS loop after the ECD, in the terminal segment of the QRS loop, resembling a “nose”, right before the T wave loop onset; this

“nose” pattern was present in all type 1 BrS patients, but in none of ER patients.

A very important arrhythmogenic pathology, the arrhythmogenic right ventricle cardiomyopathy (ARVC), has an almost definitive assessment tool in the electro-vectorcardiographic diagnosis. The end-conduction delay with low voltage and long duration to the right (forward or slightly backwards) characterizes the phenomenon with great accuracy, with the differential diagnosis being very important, since this pathology may lead to severe arrhythmias. (Figure 11)

Figure 5A: LPIFB

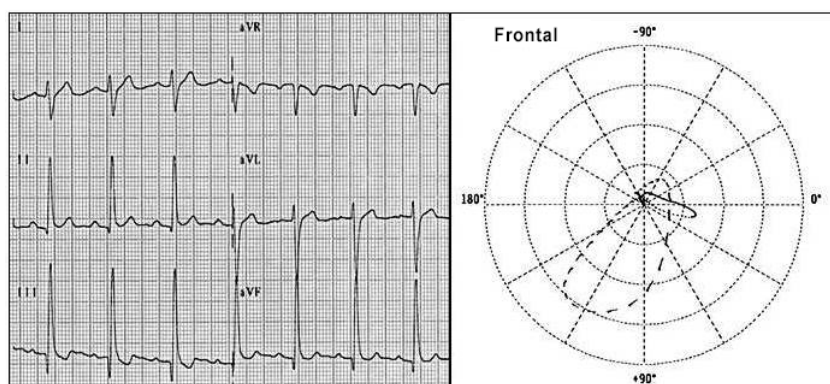


Figure 5B: LAMFB

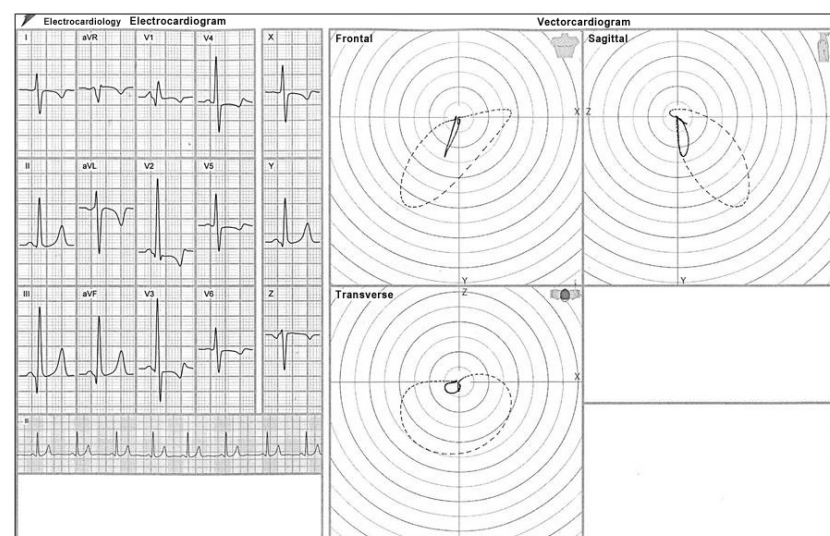


Figure 5 – Electro-vectorcardiographic aspects of LASFB - Fig. 4A of the previous item, left posteroinferior fascicular block (LPIFB) - Figure 5A and left anteromedial fascicular block (LAMFB) - Figure 5B.

ARVC sometimes presents with an aspect similar to the RBBB, although with a very low voltage that is different from that block. It can also show an ECD aspect on the right and be slightly backwards. The presence of a negative T wave in V_1 , V_2 , V_3 and left posteriorly located in the transverse plane of the ECG/VCG is crucial for an accurate diagnosis.

The ECG/VCG has been used in the follow-up of the new arrhythmia ablation procedures, as in Brugada syndrome, where it cooperates in characterizing the successful cases and differentiating them from the unsuccessful procedures. The initial and already consecrated experience of the ECG/VCG in the ventricular pre-excitation and in the ablation procedures for this syndrome has brought subsidies for the recently described observations. The Brugada syndrome has shown to be very dynamic regarding its arrhythmogenic substrate, and the ECG/VCG follow-up can be very useful to define this process.^{29,30} (Figure 12).

Author contributions

Conception and design of the research: Pastore CA, Samesima N, Facin ME; Acquisition of data: Pastore CA, Samesima N, Pereira Filho HG, Madaloso BA, Facin ME; Analysis and interpretation of the data and Critical revision of the manuscript for intellectual content: Pastore CA, Samesima N, Pereira Filho HG, Tobias NMMO, Madaloso BA, Facin ME; Writing of the manuscript: Pastore CA, Samesima N, Madaloso BA.

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.

Figure 6A: Right ventricular hypertrophy

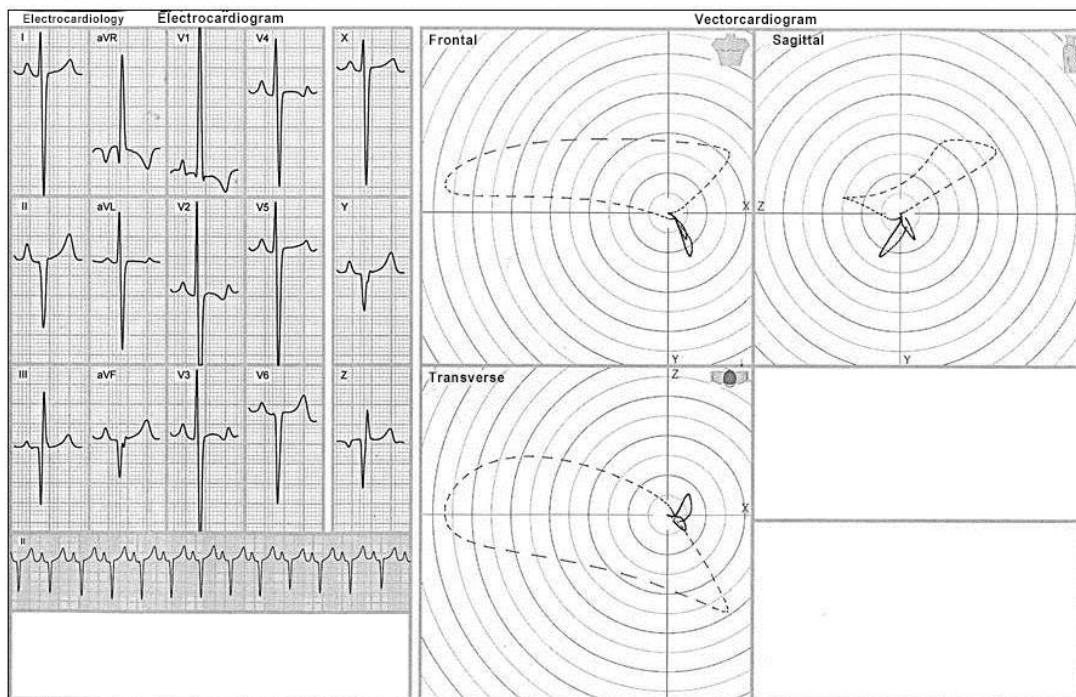


Figure 6B: Old lateral MI

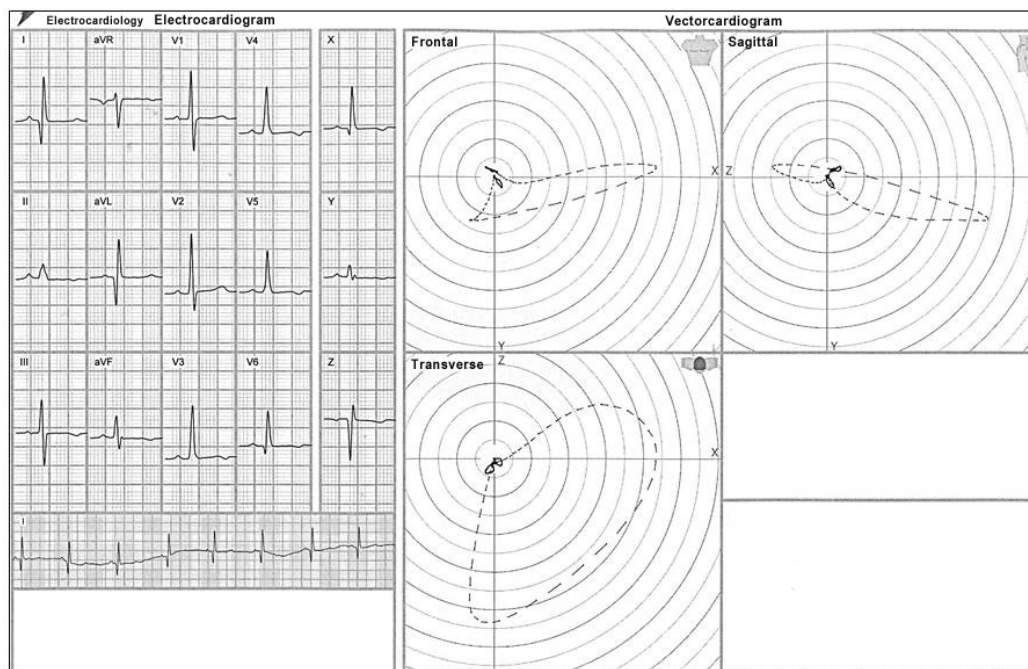


Figure 6 – Illustrations of differential diagnoses identified by the ECG/VCG in different pathologies: left anteromedial fascicular block (LAFB) - see Fig.5B; right ventricular hypertrophy (RVH) - Figure 6A; lateral infarction - Figure 6B.

Study Association

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

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Figure 6C: Ventricular pre-excitation syndrome (WPW)

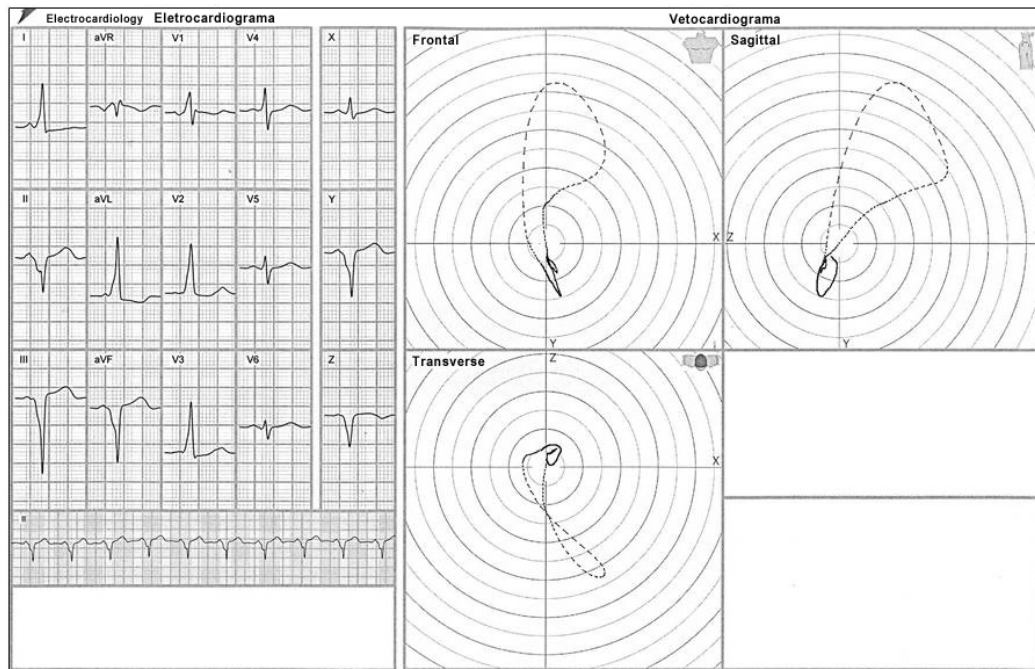


Figure 6D: Brugada syndrome

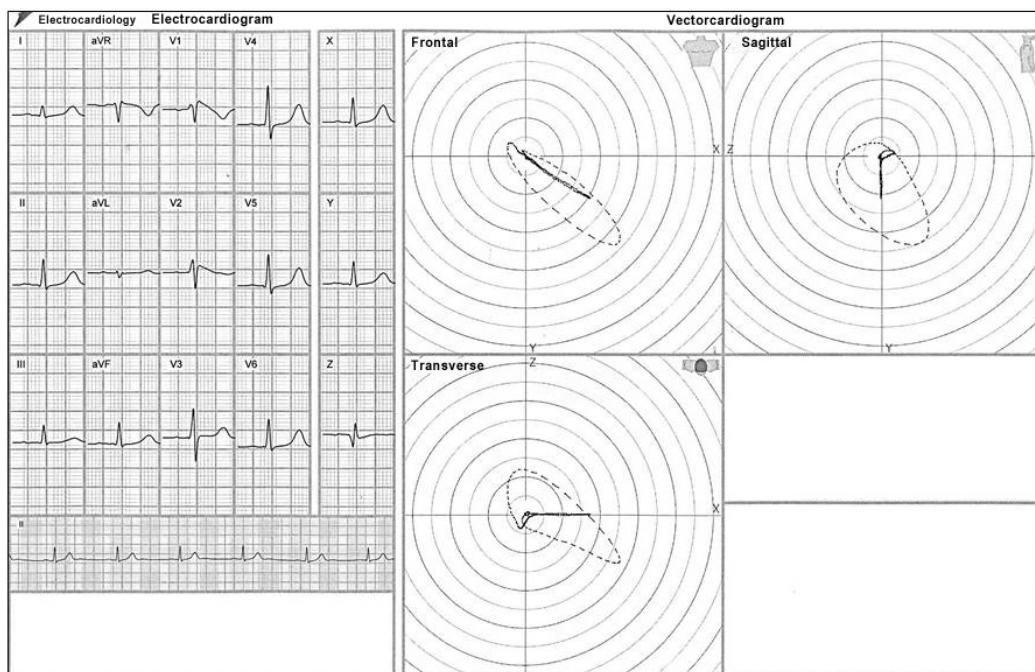


Figure 6 – Illustrations of differential diagnoses identified by the ECG/VCG in different pathologies: left anteromedial fascicular block (LAMFB) - see Fig.5B; ventricular pre-excitation syndrome (WPW) - Figure 6C; Brugada syndrome - Figure 6D.

Figure 7: LPIFB + RBBB

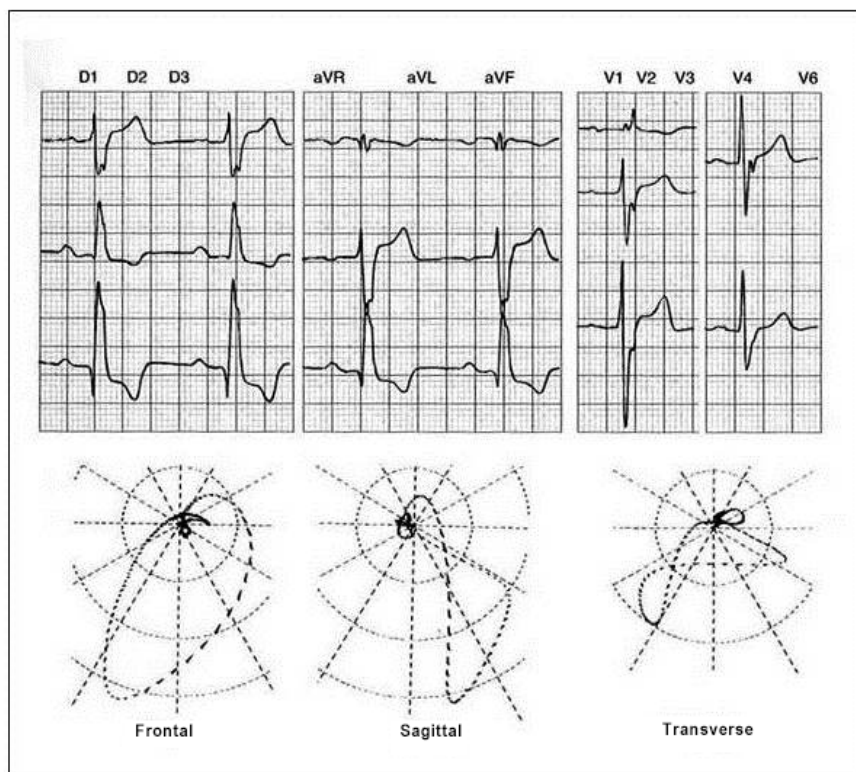


Figure 7 – Vectorcardiographic aspects of the association of LPIFB and RBBB: axis to the right in the frontal plane (LPIFB), with most of the QRS loop in the frontal plane, oriented downwardly and to the left, and the QRS loop in the transverse plane, slowly ending forwardly and to the right (RBBB).

Figure 8: End-conduction delay

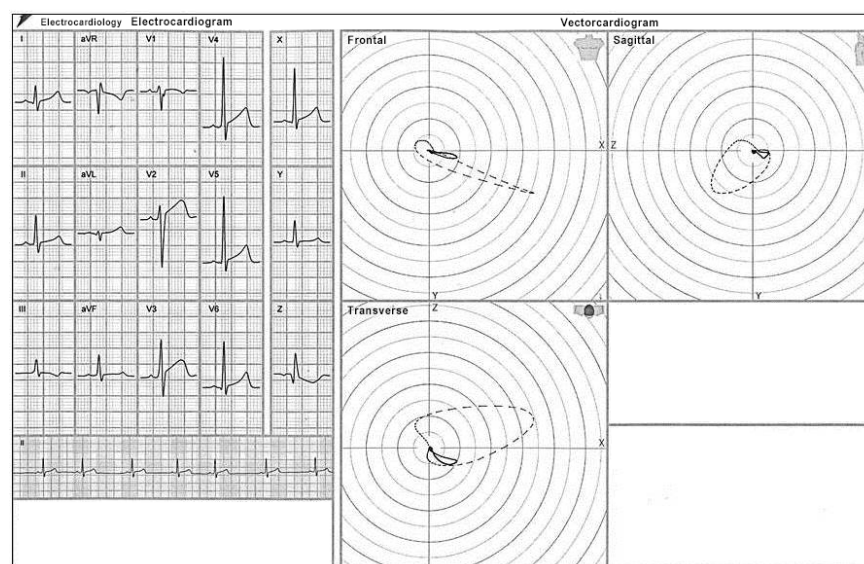


Figure 8 – Electro-vectorcardiographic aspects of the end-conduction delay.

Figure 9A: Ventricular pre-excitation

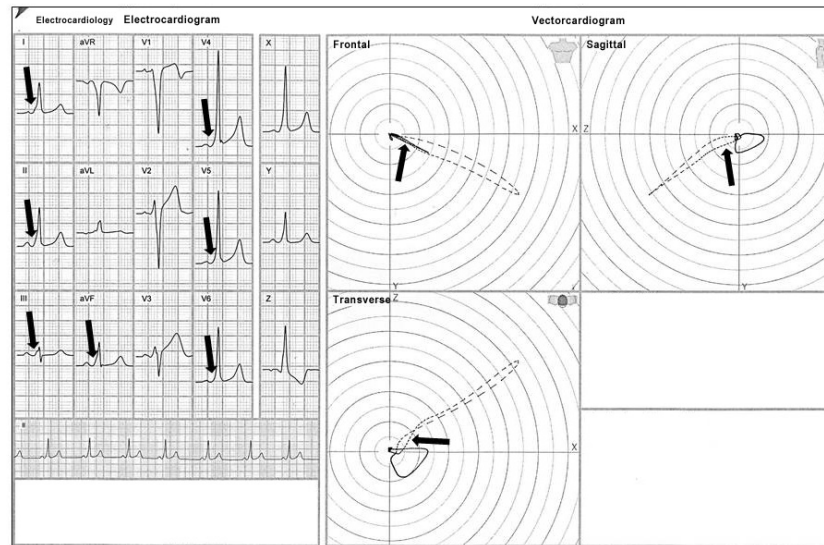


Figure 9B: Ventricular pre-excitation

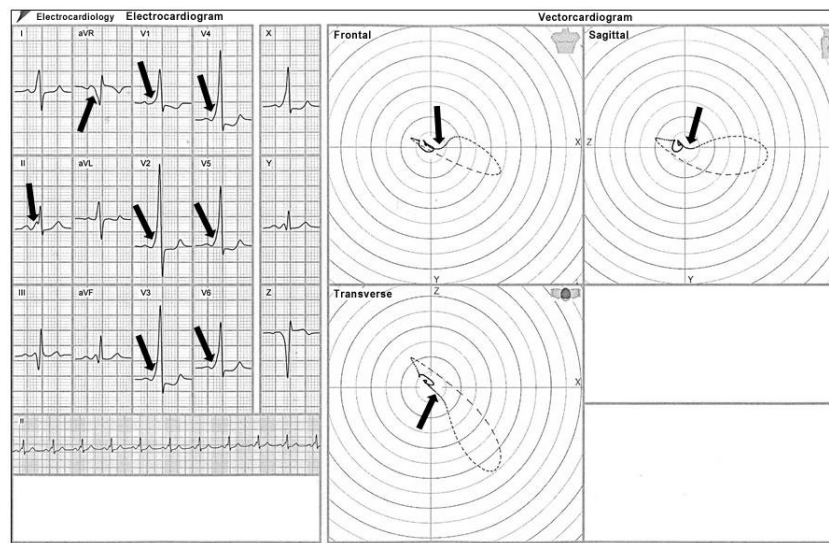


Figure 9 – (A and B). Electro-vectorcardiographic aspects of the ventricular pre-excitation, highlighting the presence of the delta wave (arrows).

Figure 10: Early repolarization

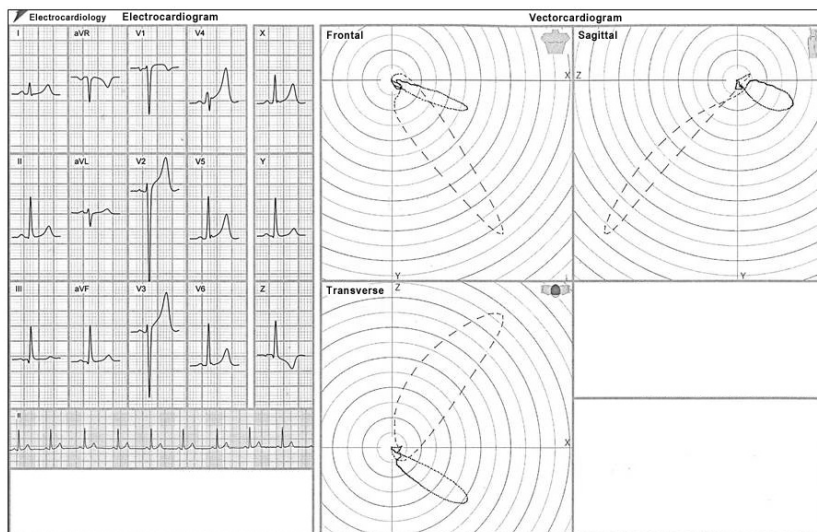


Figure 10 – Characteristic electro-vectorcardiographic aspects of the early repolarization (ER) pattern: Transverse plane: QRS loop onset with counterclockwise rotation; the ECD began posteriorly and ended anteriorly and in the left quadrant in all ER patients. At the terminal segment of the QRS loop (now with clockwise rotation), 100% of the ER group showed, at the end of QRS loop, a “fishhook” pattern.

Figure 11: Arrhythmogenic right ventricular cardiomyopathy

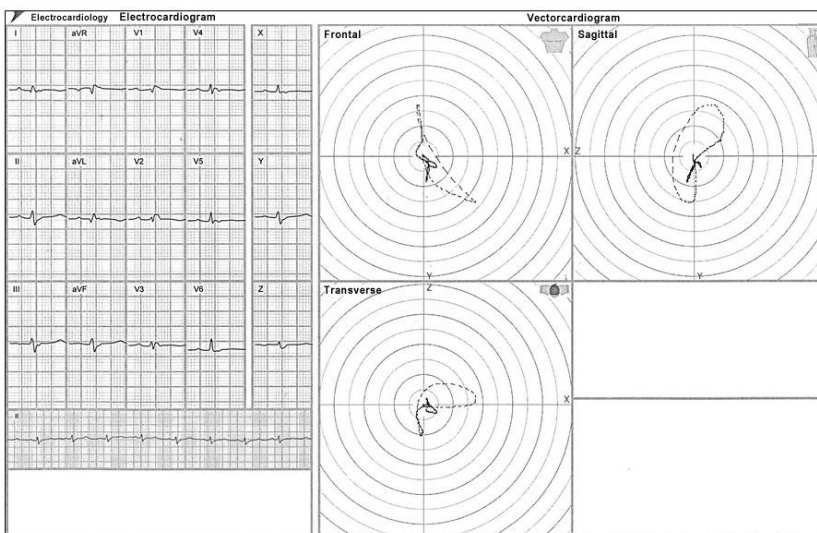


Figure 11 – Electro-vectorcardiographic aspects found in ARVC, displaying the extremely long conduction delay at the end of the QRS loop.

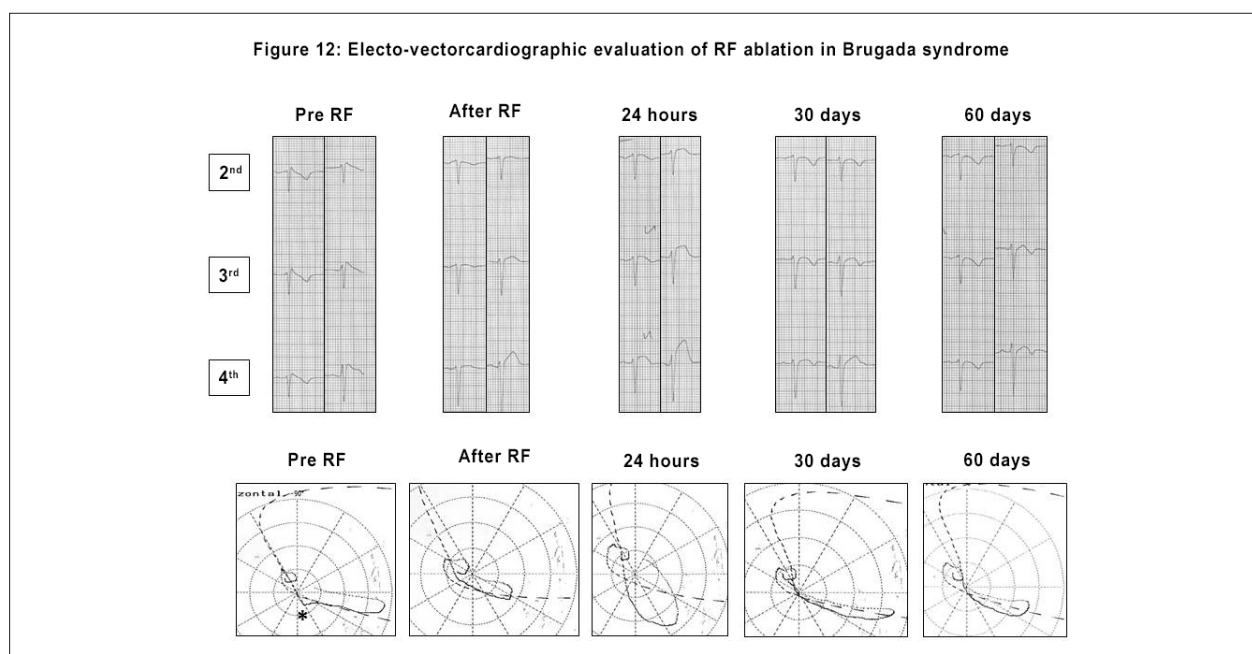


Figure 12 – Evolution of the electro-vectorcardiographic aspects after radiofrequency ablation over time in a patient with ECG-type 1 pattern of Brugada syndrome.

References

- Moffa PJ, Sanches PCR. Eletrocardiograma normal e patológico. 7ª. ed. São Paulo: Rocca; 2001.
- Strauss DG, Olson CW, Wu KC, Heiberg E, Persson E, Selvester RH, et al. Vectorcardiogram synthesized from the 12-lead electrocardiogram to image ischemia. J Electrocardiol. 2009;42(2):190-7.
- Bayes de Luna A. Clinical electrocardiography: a textbook. 4th. ed. New Jersey: Wiley-Blackwell; 2012.
- Pastore CA, Samesima N, Munerato R. ABC do ECG. 3ª. ed. São Paulo: Medcel; 2013.
- Gussak I, Antzelevich C, Wilde AAM, Powell BD, Ackerman MJ, Shen WK. Electrical diseases of the heart. London: Springer-Verlag; 2008. v.1.
- Moss AJ. Can long QT syndrome be diagnosed by vectorcardiography when the corrected QT on the resting 12-lead electrocardiogram is of normal duration? Heart Rhythm. 2017;14(6):900-1.
- Cortez D, Schlegel TT, Ackerman MJ, Bos JM. ECG-derived spatial QRS-T angle is strongly associated with hypertrophic cardiomyopathy. J Electrocardiol. 2017;50(2):195-202.
- Pastore CA, Samesima N, Tobias N, Pereira Filho HG. Eletrocardiografia atual: curso do serviço de eletrocardiografia do inCor. 3ª. ed. São Paulo: Atheneu; 2016.
- Pastore CA, Samesima N, Pereira Filho HG, Madaloso BA. Controversial and similar aspects of the Brugada and J wave patterns: the vectorcardiogram point of view. J Electrocardiol. 2016;49(3):439-45.
- Lingman M, Hartford M, Karlsson T, Herlitz J, Rubulis A, Caidahl K, et al. Value of the QRS-T area angle in improving the prediction of sudden cardiac death after acute coronary syndromes. Int J Cardiol. 2016 Sep 1;218:1-11.
- Hurst JW. Methods used to interpret the 12-lead electrocardiogram: pattern memorization versus the use of vector concepts. Clin Cardiol. 2000;23(1):4-13.
- Chou TC. When is the vectorcardiogram superior to the scalar electrocardiogram? J Am Coll Cardiol. 1986;8(4):791-9.
- Man S, Maan AC, Schalij MJ, Swenne CA. Vectorcardiographic diagnostic & prognostic information derived from the 12-lead electrocardiogram: historical review and clinical perspective. J Electrocardiol. 2015;48(4):463-75.
- Sedaghat G, Chafoori E, Waks JW, Kabir MM, Shvilkin A, Josephson ME, et al. Quantitative assessment of vectorcardiographic loop morphology. J Electrocardiol. 2016;49(2):154-63.
- Carvalho Filho ET, Moffa PF, Pastore CA, Curiati JÁ et al. Vectorcardiographic study of normal aged subjects. Arq. Bras. Cardiol. 1987;48(4):211-6.
- Sederholm M. The origin of monitoring of acute myocardial infarction with continuous vectorcardiography. J Electrocardiol. 2014;47(4):418-24.
- Correa R, Arini PD, Correa LS, Valentinuzzi M, Laciari E. Identification of patients with myocardial infarction. Vectorcardiographic and electrocardiographic analysis. Methods Inf Med. 2016;55(3):242-9.
- Warner RA, Battaglia J, Hill NE, Mookherjee S, Smulyan H. Importance of the terminal portion of the QRS in the electrocardiographic diagnosis of inferior myocardial infarction. Am J Cardiol. 1985;55(8):896-9.
- Pastore CA, Moffa PJ, Tobias NMO, Moraes AP, Nishioka SA, Chierighini JEC, et al. Bloqueios divisionais do ramo direito e áreas eletricamente inativas. Diagnóstico diferencial eletro-vetocardiográfico. Arq. Bras. Cardiol. 1985;45(5):309-17.
- Tobias NMMO, Pastore CA, Moffa PJ, Moraes AP, Lima EV, Del Nero Jr E, et al. Bloqueios divisionais do ramo direito na miocardiopatia chagásica. Arq. Bras. Cardiol. 1986;47(6):387-91.

Review Article

21. Acunzo RS, Konopka IV, Sánchez RA, Pizzarelli N, Wells FC, Baranchuk A, et al. Right bundle branch block and middle septal fiber block with or without left anterior fascicular block manifested as aberrant conduction in apparent healthy individuals: electro-vectorcardiographic characterization. *J Electrocardiol.* 2013;46(2):167-72.
22. Tranchesi J, Moffa PJ, Pastore CA, Carvalho Filho ET, Tobias NMM, Scalabrini Neto A, et al. Bloqueio da divisão anteromedial do ramo esquerdo do feixe de His nas coronariopatias: caracterização vectorcardiográfica. *Arq. Bras. Cardiol.* 1979;32(6):355-60.
23. Pastore CA, Moffa PJ, Grinberg M, Verginelli G, Ebaid M, Tranchesi J. Bloqueio da divisão posteroinferior em pós-operatório de comissurotomia aórtica e ressecção de anel fibroso subvalvar. Correlação com bloqueio atrioventricular total (relatos de casos). *Arq. Bras. Cardiol.* 1979;32(5):303-7.
24. Moffa PJ, Ferreira BMA, Sanches PCR, Tobias NMM, Pastore CA, Bellotti G. Bloqueio divisional anteromedial intermitente em paciente com insuficiência coronária. *Arq Bras Cardiol.* 1997;68(4):293-6.
25. Pastore CA, Samesima N, Kaiser E. Vectorcardiographic patterns for differential diagnosis in right end-conduction delay, early repolarisation and Brugada syndrome. *J Electrocardiol.* 2012; 46:e1-e37.
26. de Micheli A, Iturralde P, Medrano GA. On the electrical manifestations of some heart diseases associated with ventricular preexcitation. *Arch Cardiol Mex.* 2006;76(Suppl 4):S137-43.
27. Titomir LI, Trunov VG, Aidu EA, Sakhnova TA, Blinova EV. New approaches to the diagnosis of left and right ventricular hypertrophy by means of dipolar electrocardiotopography. *Anadolu Kardiyol Derg.* 2007;7(Suppl 1):29-31.
28. Pérez-Riera AR, Barbosa-Barros R, Daminello-Raimundo R, de Abreu LC, Tonussi Mendes JE, Nikus K. Left posterior fascicular block, state-of-the-art review: a 2018 update. *Indian Pacing Electrophysiol J.* 2018;18(6):217-30.
29. Samesima N, Pastore CA, Facin ME. Brugada syndrome ablation: what the vectorcardiogram can tell us? ICE/2017. Portland, EUA [Abstract]. Disponível em: www.electrocardiology.org/images/conferences/ICE_2017/schedule_2017-06-28.pdf.
30. Pastore CA, Samesima N. Brugada and J wave patterns: the role of vectorcardiography in distinguishing them. In: Brugada after RF ablation: what the vectorcardiogram can tell us? [citado 25 mar. 2019]. Disponível em: www.electrocardiology.org/images/Presentations/VCG-Brugada-Pastore.pdf.

Appendix

For additional information, please see the online version of this article.



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

Telemedicine and the Doctor/Patient Relationship

Protásio Lemos da Luz^{ID}

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

Introduction

A.C., a friendly Italian man, received coronary stents 8 years ago and had been feeling well until 3 months ago. He then had progressive breathing difficulty with tightness in his chest. He had loss of appetite and lost 4 kg in that period, but continued to work with good disposition. He had been to two hospital visits, in which he was informed that his lung was normal, based on X-ray. They had not reached final diagnosis, so he came to the office. His general appearance was normal; no abnormality was found on visual inspection. He had normal vital signs; no pallor to suggest anemia. The lungs, heart, abdomen and lower limbs were normal on examination, and resting ECG revealed no abnormalities either. As I palpated his neck, I noticed a mass on the left side. Subsequent examinations proved that a tumor compressed the trachea, which explained his respiratory difficulty. This is a typical example of a case in which only complete clinical examination leads to diagnosis. Telemedicine (TM) would not allow this, as simple inspection did not give any clues, and the clinical history suggested several possibilities, such as heart disease, pulmonary disease, diabetic decompensation, uremia or anemia.

There is now a major debate, both at the health system and at the individual telemedicine level. Telecommunication technologies have long been used in teaching, in science, in the formation of groups for the study of diseases, in the transmission of diagnostic or therapeutic medical procedures, in imaging interpretation by specialists, in teleconference with undisputed efficiency, and will not be considered here. An interesting fact: many even said that, with the Internet, medical conferences would be emptied, because everything could be seen from a distance.

That simply did not happen — medical conferences continue to attract large audiences, as much as before the online broadcasts. This proves that man is a social being and likes to live with his peers.

Telemedicine and the Doctor/Patient Relationship

Telemedicine here is considered the medical care for patients without face-to-face contact. An essential aspect is that telemedicine requires its own structures. It requires a

central station that can receive information, equipped with medical professionals ready to respond; it also requires the other end, i.e., doctors or patients providing correct data for evaluation. Recent iPhones are fundamental; they allow the exchange of images, texts; etc. Other devices record ECG, heart rate and blood pressure. And we are not far from the day that laboratory parameters will be transmitted online from skin sensors. Therefore, telecommunication systems are not an important limitation for telemedicine. Another fundamental aspect is the impact on health systems, including efficiency, costs, satisfaction and adherence of patients and doctor. As the implementation of telemedicine is relatively recent, there are only a few studies on this topic. A Cochrane review,¹ which included 93 studies and 22,047 patients, analyzed 36 studies of cardiovascular diseases, 21 of diabetes, 9 of respiratory conditions, 7 of mental health, 6 in which a specialist needed to be consulted, 3 urogenital conditions, 3 with neurological lesions, and other minor ones. Comparing telemedicine with usual care, they showed that there was no difference in overall mortality from heart failure, that hospital admissions were reduced by 64% in some studies, and increased by 60% in others. There was some evidence for improved quality of life and, in diabetes, lower glycated hemoglobin was found; greater reductions in LDL and blood pressure were also found. There were no differences between face-to-face healthcare and telemedicine in cases of mental health. Regarding costs and patient acceptance, the authors found that there was insufficient data for conclusions. The authors concluded that the efficiency of telemedicine depends on multiple factors, such as whether it is used to monitor chronic conditions and known patients or to facilitate access to diagnostic services. Worthy of note is that all studies refer to monitoring of known chronic conditions, rehabilitation training offerings, healthy life education, specialist consultations or cognitive therapy; that is, those would always refer to cases of known diagnoses rather than primary evaluations. Another analysis by Ekland et al.² included 80 studies and found that 21 of them considered effective telemedicine, 18 were promising, but still inconclusive, and the others had limited and inconsistent evidence. Bertonecello et al.³ analyzed the factors involved in the efficiency of telemedicine according to reports from 25 critically chosen reviews, comprising 15 years (2000 to 2015) of observations. Hypertension, diabetes, asthma, chronic obstructive pulmonary disease, heart failure and elderly care were included. This analysis considered several factors that may influence efficiency in telemedicine, such as the geographical location of patients, demographic characteristics and diseases (the so-called “targets”), intensity of intervention, patient perspectives and engagement, education, caregivers, organizational model and ethical and economic issues. Interestingly, none of the studies looked at all of the factors; 44% focused on the “targets” and 24% on intervention

Keywords

Physician-Patient Relations; Telemedicine; Cost Saving; Medical Care; Humanism; Patient Participation.

Mailing Address: Protásio Lemos da Luz •

Avenida Dr. Enéas de Carvalho Aguiar, 44. Postal Code 05403-000, 5andar - Bloco II sala 08, São Paulo, SP – Brazil

E-mail: protasio.luz@incor.usp.br

Manuscript received April 04/2019, revised manuscript April 10, 2019, accepted April 10, 2019

DOI: 10.5935/abc.20190117

intensity; 16% analyzed the patients' perspective. On the other hand, issues such as location, ethical issues, patient engagement or caregiver perspectives were the least addressed items. The researchers' main conclusion was that there is not yet enough concrete data on the multiple factors that influence efficiency telemedicine, and that further studies are needed to fill knowledge gaps in this area.

A major discussion is the doctor/patient relationship (DPR) in telemedicine. Traditionally, medicine has been based on the individual relationship between doctor and patient.⁴ This relationship has multiple cultural influences. In Brazil, people are very affectionate and zealous of their family relationships and their friendships. This affection extends to the doctor, which makes us all more sensitive. In the Anglo-Saxon culture, personal relationships are more distant and "colder". In practice, this means that Brazilians like to have "their doctor," rather than being treated by a stranger. The patient's trust in his/her doctor is not acquired in an instant, but in prolonged coexistence, especially in situations of risk. Patients are quite protective of their privacy, and rightly so; no one will talk about sexual impotence, relationships with spouses, children or family to a device that can record the conversation and even post it on Facebook. Likewise, an executive is not expected to report that his/her stress is a result of unsuccessful business; if this is announced, the situation will only get worse. How is it possible to convey affection, understanding, commitment, compassion, human warmth at last – without looking into the patient's eyes? Another significant point is body language. It is well known to psychologists that about 80% of messages one person conveys to others is not verbal;⁵ it is conveyed through body posture, voice intonation, the way the person looks, how they move their hands and arms, the way they sit, whether they smile or not, and whether their smile is spontaneous or not. In short, there are whole books dedicated to this topic.⁶ Also, when the jury meets to judge major crimes, witnesses and defendants are heard personally. The purpose of that is precisely for the jurors to assess the authenticity of the accounts. Doctor/patient contact has a similar meaning. Both the doctor evaluates the patient and the patient evaluates the doctor. It is questionable whether an image could replace that personal contact with the same precision.

In a more general view, how do you know if the doctor on the other end of the line has the authority to give an opinion on that case? Countless patients seek the opinion of renowned doctors, even after they have gone through a number of other doctor's visits. This only emphasizes one of the basic principles on which medicine is based: trust. In addition, does telemedicine lessen medical error? According to J. Groopman⁷ – doctors make mistakes in 15% of the cases on average. That's a high percentage! The impact that telemedicine will have on this is unknown; there is no data.

Another key aspect is compensation. There are no established criteria; this should be a reason for wide discussion, as there are several points to be considered, such as public healthcare, health insurance and private patients. In this particular case, many medical entities and providers should participate.

Another point to consider is who/which entities should establish the rules of telemedicine practice. Usually, the Federal Medical Council, medical societies, medical colleges and patient representatives should be heard. So far, patients have been systematically excluded from similar discussions. This needs to be fixed. After all, patients are the goal of medical actions, they take the risks and pay for healthcare. Besides, this is critical – in the case of telemedicine, as in all medical procedures, the patient must explicitly agree with the process, as it involves potential privacy and confidentiality issues. Along these lines, patients' rights to privacy, alternatives, potential risks and benefits must be preserved. As previously said, the patient does not always accept new technologies like the telemedicine. It is necessary to be clear that they have freedom of choice.

Therefore, which stance should we take on the current medical practice? Conceptually speaking, it is clear that telemedicine is here to stay. It is simply a matter of adapting it to medical practice. Having said this, I believe that:

- a) the first visit must be in person; neither anamnesis nor physical examination can be eliminated – this is indispensable for the diagnosis and referral of the case; regular re-evaluations are also required.
- b) On the other hand, telemedicine may be useful in several circumstances, including the ones below, among others:
 - b.1. in the reassessment and monitoring of known patients, to adjust medications, answer simple questions, check for adherence and others.
 - b.2. to share information on additional tests, especially when these are normal. The patient does not have to go back to the office just to know that everything is normal; they should lead a normal life and be re-evaluated within a year, and so on.
 - b.3. patients in remote regions where there are no medical resources; such people can receive general guidance as in cases of diarrhea, fractures, childbirth, trauma and other ordinary situations. General guidance will be at the discretion of the central physician.
 - b.4. to avoid unnecessary hospital visits, such as to get results of simple tests, prothrombin time, in which case medical advice can be given at a distance, saving time and discomfort in addition to reducing costs.
 - b.5. to advise on the choice of specialists for specific cases.
 - b.6. to reduce hospitalization time – this is perfectly possible as long as the patient is monitored after discharge.
 - b.7. in cases where there is a long waiting for a visit, as in public healthcare, follow-up by telemedicine may facilitate or redirect the case.

In short, any innovation can bring progress and also new challenges. With telemedicine, it is not different. The concept, however, needs to be well understood. Telemedicine has not come to fully replace traditional practice. It is here to perfect it. The doctor's responsibility remains the same; the doctor is the one who will make the main decisions.

We should use the best of the two worlds: preserving humanism in medicine and using new technologies to improve medical care. This is possible; it only depends on some adjustments that are evidently possible. However, further studies are still needed to answer important questions such as those mentioned above. These questions include patient acceptance, the effectiveness of telemedicine in specific clinical conditions and the impact on the health system as a whole. One possibility that cannot be ruled out is that telemedicine and the telecommunication media may become so efficient in the future, to the point that doctor/patient relationships are drastically changed, and what is causing concern today is outweighed by other much more significant advantages. This has happened to iPhones and the social media: no one writes letters anymore. And no one misses them.

However, while cost reduction in the health system is an important element, on the other, cost reduction alone cannot be the only standard of analysis for a new technology such as telemedicine. It is always important to be aware of the benefits for the patients.

Author contributions

Conception and design of the research and Writing of the manuscript: Luz PL.

Potential Conflict of Interest

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

Sources of Funding

This study was funded by Bradesco S.A.

Study Association

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

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. Flodgren G, Rachas A, Farmer AJ, Inzitari M, Shepperd S. et al. Interactive telemedicine: effects on professional practice and health care outcomes. Cochrane Database of Systematic. 2015; 2015;9:CD002098.
2. Ekland AG, Bowes A, Flottorp S. Effectiveness of telemedicine: a systematic review of reviews. Int J Med Inform. 2010;79(11):736-71.
3. Bertonecello C, Colucci M, Baldovin T, Buja A, Baldo V. How does it work? Factors involved in telemedicine home-interventions effectiveness: a review of reviews. PloS One. 2018 Nov 15; 13(11):e0207-332
4. Luz PL. Nem só de ciência se faz a cura. São Paulo: Atheneu; 2001.
5. Pease A, Pease B. Desvendando os segredos da linguagem corporal. Rio de Janeiro: Sextante; 2005.
6. Dimitrius Jo-E, Mazzarella WP. Decifrar pessoas: como entender e prever o comportamento humano. São Paulo: Alegro; 2000
7. Groopman JE. Como os médicos pensam. Rio de Janeiro: Sinergia - Agir; 2009



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

Case 4/2019 – Pulmonary Atresia, Ventricular Septal Defect, and Systemic-Pulmonary Collateral Circulation developing after prior Blalock-Taussig, in a Symptomatic 47-Year-Old Adult

Edmar Atik,^{1B} Maria Angélica Binotto, Alessandra Costa Barreto, Walther Ishikawa

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

Clinical data

The patient had no symptoms from birth to young adulthood, when he developed more severe hypoxia, which required a Blalock-Taussig anastomosis on the right. Five years ago, worsening of hypoxia was again observed, with hemapheresis every 6 months, in addition to fatigue on small to medium exertion and with associated ventricular dysfunction. He used f warfarin, carvedilol and enalapril, in addition to nasal oxygen at night.

Physical examination: good overall status, eupneic, moderate cyanosis in the extremities, marked digital clubbing, normal pulses in the 4 limbs. Weight: 68 kg, Height: 170 cm, right upper limb blood pressure: 125 x 90 mmHg, HR: 80 bpm, O₂ saturation = 82%, Hg = 24.5 g / L, Hct = 75%.

Precordium: apex beat palpable outside the left hemiclavicular line, with clear systolic impulses at the left sternal border (LSB). Hyperphonic heart sounds, inconstant split 2nd heart sound, discrete systolic murmur along the LSB, and moderate continuous murmur at the right sternal border and right dorsum. The liver was not palpable, and the lungs were clear.

Complementary examinations

Electrocardiogram: Sinus rhythm, signs of right cavity overload, with apiculate P wave and high in the left precordial, and in I and II leads (AP = +40°), and QRS complex showing predominance of S waves from V3 to V6 and axis deviated to the right (AQRS = + 180°). The T wave was negative in the precordial leads (AT = +50°) (Figure 1).

Chest X-ray: Discrete enlargement of the cardiac area due to elongated and rounded left ventricular arch and excavated middle arch (CTI = 0.53). The aortic arch is on the right, with an increased pulmonary vascular network in the hila and lower lobes (Figure 1).

Echocardiogram: Normal atrioventricular connection, pulmonary atresia and perimembranous 30-mm ventricular septal defect and single outflow tract with aorta (42 mm),

overriding the interventricular septum for more than 50%. The right atrium is very dilated (33 cm² area) and the left atrium (38 mm) is discretely dilated. The right ventricle (40 mm) is dilated and hypertrophic, with moderate dysfunction. The left ventricle (40 mm) is hypertrophic with 57% function by the Simpson method. Blalock-Taussig anastomosis was not visualized.

Myocardial nuclear magnetic resonance imaging:

The diagnosis was confirmed with similar measurements. RVEDV = 120 mL/m² and RV function = 37%. LVEDV = 94 mL/m² with LV function = 54%. Late enhancement was observed in the lower and septal region.

Angiotomography: It showed marked hypoplasia of the pulmonary arteries, especially to the right and the well-developed intraparenchymal pulmonary artery tree, mainly visible in the lower lobes, due to large systemic-pulmonary collaterals, on the right and left, from the descending aorta, with the aortic arch to the right (Figure 2).

Holter: Frequent ventricular extrasystoles (<1% of the total), without supraventricular or ventricular tachycardia.

Clinical diagnosis: Pulmonary atresia, ventricular septal defect and systemic-pulmonary collateral circulation with previous Blalock-Taussig occlusion, with right ventricular dysfunction and signs of marked progressive hypoxia in later adulthood.

Clinical reasoning: There were clinical elements leading to a diagnosis of congenital heart disease, with arterial malposition considering the hyperphonic heart sounds and pulmonary atresia in the presence of a continuous clear murmur at the right upper sternal border and right dorsal region, indicating systemic-pulmonary collaterals due to pulmonary perfusion. The right ventricular overload on the electrocardiogram demonstrates the predominance of this ventricle given the correlated hypertrophy. The discrete degree of hypoxia with oxygen saturation of approximately 80% is associated with the increased pulmonary vascular network on the chest X-ray. But even in adults, it provides a considerable increase in red blood cells and their levels in relation to that of serum. The diagnosis of the anomaly was well established by the echocardiography, MRI and mainly by the angiography.

Differential diagnosis: Other heart diseases that accompany ventricular septal defect and pulmonary atresia show other features that differentiate them in the usual complementary exams, such as the double inlet right or left ventricle, atrioventricular valve atresia, corrected transposition of the great arteries, and in rarer diseases.

Conduct: Despite the balance of the pulmonary and systemic flows over time, with signs of hypoxemia and myocardial dysfunction, the need to increase pulmonary

Keywords

Pulmonary Atresia; Heart Septal Defects, Ventricular; Collateral Circulation; Adult; Clinical Evolution.

Mailing Address: Edmar Atik •

Consultório privado. Rua Dona Adma Jafet, 74, conj.73, Bela Vista.

Postal Code 01308-050, São Paulo, SP – Brazil

E-mail: conatik@incor.usp.br

DOI: 10.5935/abc.20190121

Clinicoradiological Correlation

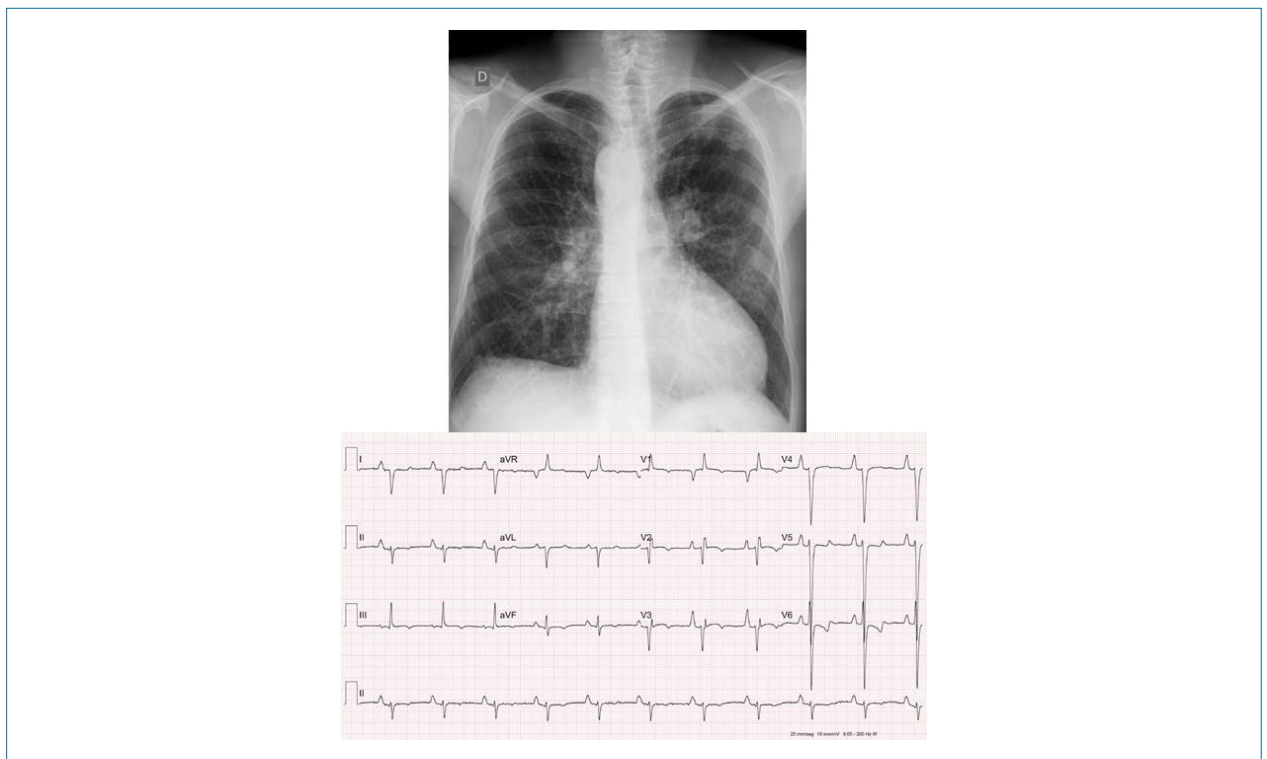


Figure 1 – Chest X-ray showing enlarged cardiac area with ventricular dominance and increased pulmonary vascular network. Electrocardiogram shows right cavity overload.

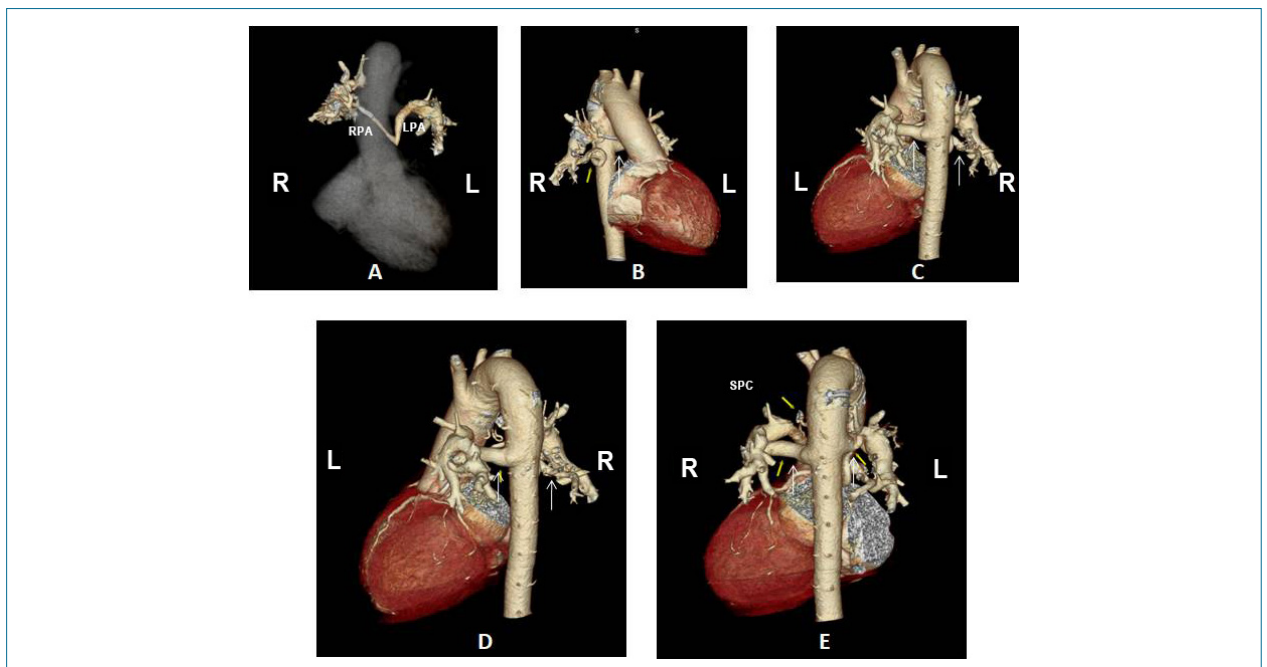


Figure 2 – Angiotomography depicting pulmonary artery hypoplasia, especially the right one in A, and the well-developed intraparenchymal pulmonary artery tree due to large systemic-pulmonary collaterals (arrows) on the left and on the right, from the descending aorta in B, C, D, and E, with aortic arch on the right. RPA: right pulmonary artery; LPA: left pulmonary artery; SPC: systemic-pulmonary collateral; R: right; L: left.

Clinicoradiological Correlation

flow to improve quality of life with better physical tolerance is presumed. The consideration of the expectant conduct would not be totally ruled out considering the patient's age, with other development risks.

Comments: The natural evolution of this patient until the adult age highlights unfavorable elements, considering that the previous palliative surgery, the Blalock-Taussig anastomosis, occluded spontaneously. Hence, it certainly did not influence this temporal evolution. They are represented in this case by the enlargement of the heart cavities, the right ventricular hypertrophy with RV dysfunction and the pronounced increase

in the concentration of red blood cells, which repeatedly required hemapheresis. The doubt persists regarding the performance of another systemic-pulmonary anastomosis to further prolong life and improve quality of life. On the other hand, the expectant conduct should also be considered in this case, given the high and considerable surgical risk in this age group.¹

The question is, in similar cases in childhood, whether it would be more convenient to attempt an earlier correction. Undoubtedly, it should always be considered at different times to create an anatomic shape that is adequate and favorable to blood dynamics.²

References

1. Presnell LB, Blankenship A, Cheatham SL, Owens GE, Staveski SL. An overview of pulmonary atresia and major aortopulmonary collateral arteries. *World J Pediatr Congenit Heart Surg.* 2015; 6(4):630-9.
2. Liava'a M, Brizard CP, Konstantinov IE, Robertson T, Cheung MM, Weintraub R, d'Udekem Y. Pulmonary atresia, ventricular septal defect, and major aortopulmonary collaterals: neonatal pulmonary artery rehabilitation without unifocalization. *Ann Thorac Surg.* 2012;93(1):185-91.



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

Vasospasm during Exertion: New Pathophysiological Insights

Gonzalo Navarrete,¹ Eduardo Pozo, Fernando Rivero, Teresa Bastante, Luis Jesús Jiménez-Borreguero, Fernando Alfonso
Hospital Universitario La Princesa. Madrid, Madrid – Spain

A 69-year-old male with hypertension, dyslipemia and no previous cardiovascular disease presented a transient ST-segment elevation on electrographic (ECG) monitoring during a planned ureteroscopy. The patient remained asymptomatic during the postoperative period. He only referred very sporadic episodes of effort chest pain in the last years without progression or events at rest. Given the lack of ECG registry, an exercise stress echocardiogram was indicated. The study was clinical and echocardiographically positive for inducible ischemia, with hypokinesia of the mid and apical anterior wall segments at peak exercise without ECG changes. With the documentation of ischemia in the left anterior descending coronary artery (LAD) territory, a coronary angiogram was performed. Only a mild lesion in the proximal LAD was demonstrated. However, a severe lesion in the proximal right coronary artery (RCA) (Figure 1A and 1B), was treated with a bioabsorbable scaffold (Figure 1C), despite the absence of inducible ischemia demonstration in that territory. The patient was discharged on dual antiplatelet treatment, betablockers and statins and remained asymptomatic without new episodes of chest pain. Six months later, during another ureteroscopy, a new episode of transient ST-segment elevation was observed on ECG monitoring. At that time, a treadmill test was performed showing marked transient ST-segment elevation in V1-V4 leads (Figure 2A). Repeated coronary angiography demonstrated the good result of the previously implanted stent in RCA and persistence of a mild plaque in the proximal LAD. Due to the previously documented ECG changes in the right precordial leads, a pressure guide was performed in the proximal LAD, which ruled out the functional significance of this lesion (iFR 0.88; FFR 0.87 with 600 mcg Adenosine) (Figure 2B). In the light of the discordant ECG, echocardiographic and angiographic findings, a vasospasm test with intracoronary methylergonovine (20 mcg) was eventually carried out. This test was positive with angina reproduction and a significant reduction in LAD vessel diameter up to 90% diameter stenosis (Figure 2C) with a concomitant Pd/Pa value of 0.60 (Figure 2D). Finally, the patient could be discharged under treatment with nitrates and calcium channel blockers, remaining asymptomatic at 1-year follow-up. An exercise stress echocardiogram was negative for inducible ischemia and repeated ureteroscopy procedures were uneventful.

Keywords

Coronary Vasoospasm/physiopathology; Coronary Vessels; Myocardial Ischemia; Coronary Angiography; Electrocardiology; Echocardiography.

Mailing Address: Fernando Alfonso •
C/ Diego de León 62, 28006, Madrid – Spain
E-mail: falf@hotmail.com

Manuscript received October 25, 2017, revised manuscript October 02, 2018, accepted October 02, 2018

DOI: 10.5935/abc.20190090

Coronary artery spasm (CAS) that clinically represents variant or Prinzmetal angina,¹ is caused by a sudden intense vasoconstriction of an epicardial coronary artery, which can appear both at the site of stenosis and in angiographically normal coronary arteries. CAS during exertion is an atypical presentation of this clinical entity, firstly described by Cheng et al in 1973, as the “variant of the variant”.² The pathophysiology of CAS during exercise has not been completely clarified yet. However, it is well established that exercise can induce CAS in patients with variant angina, as demonstrated in small groups of patients subjected to supine bicycle exercise on the cardiac catheterization table.³ Exercise stress echocardiogram induced ST-segment elevation with striking discordance between the echocardiographic and angiographic findings is a rare condition that may be a result of severe CAS. To our knowledge, however, echocardiographic abnormalities unraveled during exercise echocardiography in patients with variant angina have not been previously described. Furthermore, there is no previous evidence of the potential value of physiological assessment of lesion severity, with pressure wire quantification of FFR and iFR, during CAS induction. Physiological assessment of the dynamic changes detected on Pd/Pa immediately after methylergonovine injection may be of potential clinical value in this vexing clinical setting.

This case represents an atypical presentation of variant angina in a patient with coronary artery disease. We hypothesize that hyperventilation, both during exercise and during anesthesia, might act as a trigger for CAS. In these situations, ischemia was nicely shown with noninvasive (exercise stress echocardiogram) as well as invasive diagnostic techniques (methylergonovine test). Provocative spasm testing continues to be a clinically useful tool to diagnose vasospastic angina validated in previous studies with a sensitivity of $\geq 90\%$ and specificity $\geq 97\%$.⁴ In summary, our findings illustrate the possibility of CAS even in patients with significant coronary artery disease and exertional chest pain. Further diagnostic insights are of major clinical value when discordance between electrocardiographic, echocardiographic and angiographic findings persists.

Author contributions

Conception and design of the research: Navarrete G, Pozo E, Rivero F, Jiménez-Borreguero LJ, Alfonso F; Acquisition of data: Navarrete G, Rivero F, Bastante T; Analysis and interpretation of the data: Navarrete G; Writing of the manuscript: Navarrete G, Pozo E, Alfonso F; Critical revision of the manuscript for intellectual content: Pozo E, Rivero F, Bastante T, Jiménez-Borreguero LJ, Alfonso F.

Potential Conflict of Interest

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

Case Report

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.

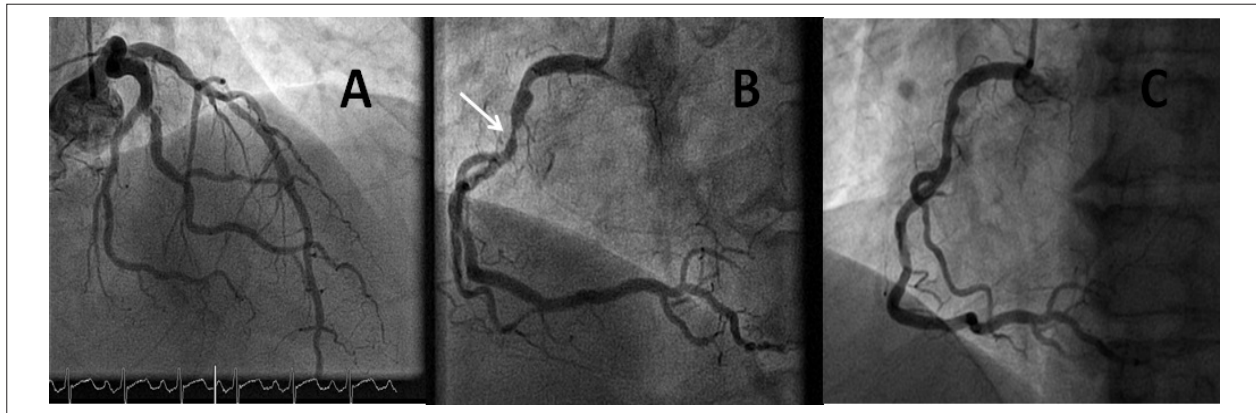


Figure 1 – ICA after stress echocardiogram. A) ICA in caudal right oblique projection that demonstrates mild plaque in proximal LAD. B) ICA in left anterior oblique projection that showed severe obstruction in RCA (arrow). C) ICA in left anterior oblique projection after the implant of bioabsorbable scaffold in RCA. ICA: invasive coronary angiography LAD: left anterior descending artery. RCA: right coronary artery.

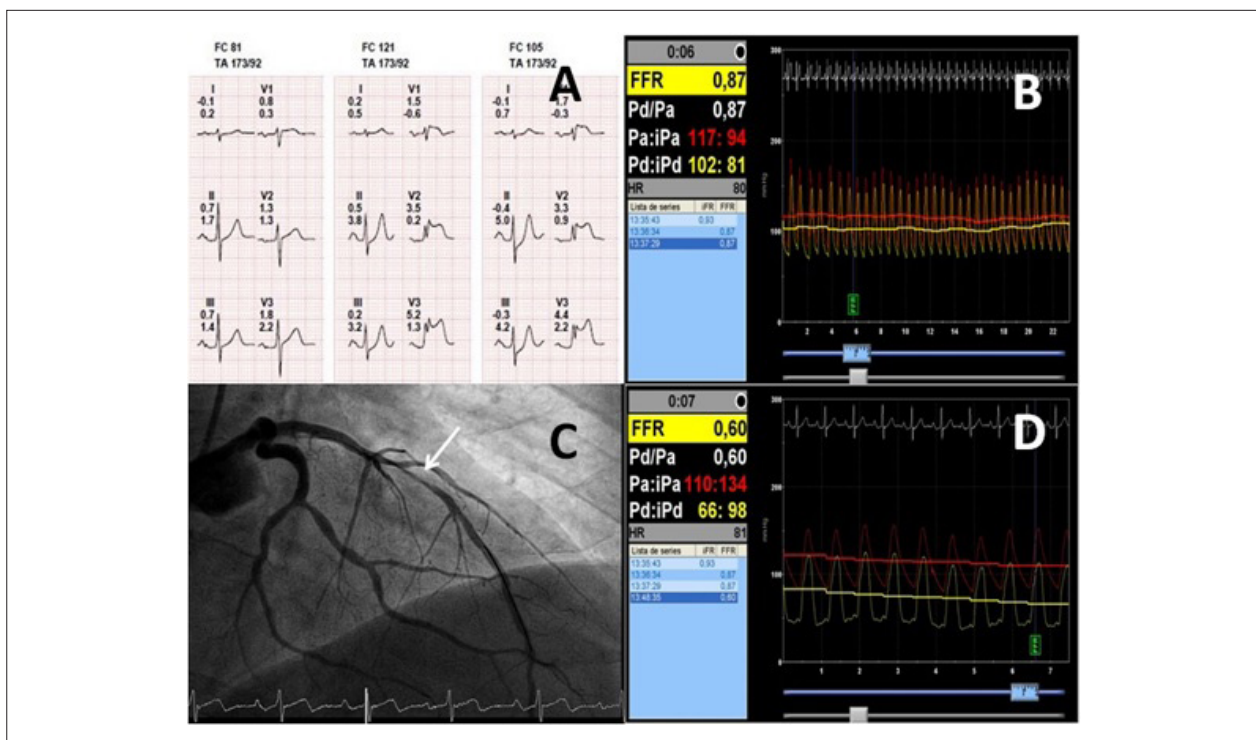


Figure 2 – ECG during treadmill test, pressure guide pre and post vasospasm test, and ICA post vasospasm test. A) ECG during treadmill test showed ST elevation in V1-V4 leads. B) FFR value in proximal LAD which discarded functional significance of this lesion. C) ICA after methylergonovine injection confirmed focal vasospasm in LAD. Panel D: FFR value after methylergonovine injection that demonstrated functional significance of vasospasm. ICA: invasive coronary angiography; FFR: fractional flow reserve; LAD: left anterior descending artery.

References

1. Prinzmetal M, Kenamer R, Merliss R, Wada T, Bor N. Angina pectoris. The variant form of angina pectoris. *Am J Med*, 1959 Sep; 27:375-38.
2. Cheng TO, Bashour T, Kelser GA Jr, Weiss L, Bacos J. Variant angina of Prinzmetal with normal coronary arteriograms. A variant of the variant. *Circulation*. 1973;47(3):476-85.
3. Fuller CM, Raizner AE, Chahine RA, Nahormek P, Ishimori T, Verani M, et al. Exercise induced coronary arterial spasm: angiographic demonstration, documentation of ischemia by myocardial scintigraphy and results of pharmacologic intervention. *Am J Cardiol*. 1980;46(3):500-6.
4. Beltrame JF, Crea F, Kaski JC, Ogawa H, Ong P, Sechtem U, et al. The Who, What, Why, When, How and Where of Vasospastic Angina. *Circulation*. 2016; 80(2):289-98.



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

Prolonged PR Interval and Outcome in Cardiac Resynchronization Therapy

Jakrin Kewcharoen¹ and Chanavuth Kanitsoraphan

University of Hawaii Internal Medicine Residency Program, Honolulu, HI – USA

Dear Editor

We read the article “Baseline Prolonged PR Interval and Outcome of Cardiac Resynchronization Therapy: A Systematic Review and Meta-analysis” by Rattanawong et al.¹ with great interest. The authors investigated the effect of prolonged PR interval on composite outcome among patients who received cardio resynchronized therapy. The authors conclude that prolonged PR is associated with worse outcome in this population.

I would like to commend the authors for performing a systematic review and meta-analysis on this topic. The effect of prolonged PR interval was well-known in the general population. However, in this specific population, the answer is unclear and was in needed for answers, given almost half of the patients with cardiac resynchronization therapy (CRT) had 1st degree AV block.² Although several previous studies reported a negative impact on the cardiovascular outcome, they were retrospective cohort and was limited by a relatively small number of participants. Nevertheless, the authors demonstrated a good systematic review and performed the random-effect model with statistical perfection.

However, as the authors mentioned in the article, this meta-analysis has a limitation regarding the number of the included studies. Also, there is a difference in the cut-point

for prolonged PR interval among the included studies. Although the study by Friedman et al. was the only study that used the cut-point of 230 ms instead of 200 ms, they have the most included participants and has the most weight percentage in all three forest plots. We thought that this is a crucial point as a change in risk ratio of the study by Friedman et al.³ could potentially change the overall pooled RR of the meta-analysis.

There are two additional studies that we thought could be included in the meta-analysis that could affect the outcome of this meta-analysis. Studies by Stockburger et al.⁴ and Lin et al.⁵ evaluated the effect of PR interval in patients with CRT.

Stockburger et al.⁴ performed a post hoc analysis from the Multicenter automatic defibrillator implantation trial with cardiac resynchronization therapy (MADIT-CRT) trial. The authors found that patients with CRT who had short PR interval (< 230 ms) generally had worse outcome regarding heart failure and all-cause mortality, regardless of the QRS duration, although the authors did not directly compare the prolonged PR interval to normal PR interval.

Another study by Lin et al.⁵ was based on the secondary analysis of The Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial. The authors reported that the outcome of all-cause mortality was reduced in both normal and prolonged PR interval group when compared to medical therapy alone, but more so in the prolonged PR interval group. Moreover, in a multivariable Cox model, progressively longer baseline PR interval, as a continuous variable, was associated with an increasingly greater reduction in the primary outcome.

Given that results from these two studies reported a positive correlation between PR interval and cardiovascular outcome, including the data from the two studies could potentially change the outcome of this meta-analysis.

Keywords

Heart Failure; Cardiac resynchronization Therapy/methods; Meta-Analysis; Atrioventricular Block; Heart Conduction, System

Mailing Address: Jakrin Kewcharoen •

1212 Nuuanu ave, Honolulu, HI, 96817 - USA

Email address: jakrin@hawaii.edu

Manuscript received March 24, 2019, revised manuscript April 24, 2019, accepted April 24, 2019

DOI: 10.5935/abc.20190101

References

1. Rattanawong P, Prasitlumkum N, Riangwiwat T, kanjanahattaki N, Vuthikraivit W, Chongsathidkiat P, et al. Baseline Prolonged PR Interval and Outcome of Cardiac Resynchronization Therapy: A Systematic Review and Meta-analysis. *Arq Bras Cardiol.* 2018;111(5):710-9.
2. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, et al. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *The New England journal of medicine.* 2004;350(21):2140-50.
3. Friedman DJ, Bao H, Spatz ES, Curtis JP, Daubert JP, Al-Khatib SM. Association between a prolonged PR interval and outcomes of cardiac resynchronization therapy: a report from the National cardiovascular Data-Registry. *Circulation.* 2016;134(21):1617-28.
4. Stockburger M, Moss AJ, Klein HU, Zareba W, Goldenberg I, Biton Y, et al. Sustained clinical benefit of cardiac resynchronization therapy in non-LBBB patients with prolonged PR-interval: MADIT-CRT long-term follow-up. *Clin Res Cardiol.* 2016;105(11):944-52.
5. Lin J, Buhr KA, Kipp R. Effect of PR Interval on Outcomes Following Cardiac Resynchronization Therapy: A Secondary Analysis of the COMPANION Trial. *J Cardiovasc Electrophysiol.* 2017;28(2):185-91.

Reply

We appreciate the author's comments on our original article "Baseline Prolonged PR Interval and Outcome of Cardiac Resynchronization Therapy: A Systematic Review and Meta-analysis".¹ We agree with the authors that the effect of PR interval in cardiac resynchronization therapy (CRT) population is unknown, and therefore we conducted a systematic review and meta-analysis on this topic.

We agree that the study by Friedman et al.² has the most included participants and has the most percentage in all three forest plots. However, to evaluate the effect of Friedman et al.,² we performed a sensitivity analysis by excluding one study at a time which is shown in Supplementary Document 2 in the original article.¹ After excluding Friedman et al.,² there was no significant change of the risk ratio of composite outcome (risk ratio = 1.19, 95% confidence interval: 1.04-1.36), all-cause mortality (risk ratio=1.53, 95% confidence interval: 1.23-1.91), and heart failure hospitalization (risk ratio = 1.6, 95% confidence interval: 1.06-2.42).¹ The meta-analysis pooled result still has a statistically significant risk ratio even if we exclude the study by Friedman et al.² Therefore, a prolonged PR interval still predicts the outcomes of CRT regardless of the results of the study by Friedman et al.²

We appreciate the author's recommendation to include the study by Stockburger et al.³ and Lin et al.⁴ Both studies were included from our comprehensive search and both full-text articles were reviewed. However, both studies were excluded from our systematic review and meta-analysis for the following reasons.

The study by Lin et al.⁴ was excluded from our systematic review and meta-analysis due to an inappropriate comparison as demonstrated in Figure 1 of our original article.¹ Their objective is to compare the outcomes between CRT and optimal pharmacologic therapy stratified by PR interval. Our meta-analysis compared the outcome of prolonged PR interval versus normal PR interval only in CRT patients.

Similarly, the study by Stockburger et al.³ was also excluded from our systematic review and meta-analysis due to an inappropriate comparator. Stockburger et al.³ reported that patients with prolonged PR interval derived clinical benefit with reduction in heart failure or death from CRT when compared to an implantable cardioverter defibrillator.³ Therefore, their comparison was different from our study, which was prolonged PR interval versus normal PR interval in CRT patients.

Our systematic review and meta-analysis used comprehensive search methodology and strict inclusion and exclusion criteria; therefore our results are robust. We showed that a prolonged PR interval in CRT patients is significantly associated with an increased risk for all-cause mortality, composite outcome, and HF hospitalization when compared to normal PR interval in CRT patients.¹

**Rattanawong, Pattara
Prasitlumkum, Narut
Riangwiwat, Tanawan.
Kanjanahattakij, Napatt
Vutthikraivit, Wasawat**

References

1. Rattanawong P, Prasitlumkum N, Riangwiwat T, Kanjanahattakij N, Vutthikraivit W, Chongsathidkiet P, et al. Baseline Prolonged PR Interval and Outcome of Cardiac Resynchronization Therapy: A Systematic Review and Meta-analysis. *Arq Bras Cardiol*. 2018;111(5):710-9.
2. Friedman DJ, Bao H, Spatz ES, Curtis JP, Daubert JP, Al-Khatib SM. Association Between a Prolonged PR Interval and Outcomes of Cardiac Resynchronization Therapy: A Report From the National Cardiovascular Data Registry. *Circulation*. 2016;134(21):1617-28.
3. Stockburger M, Moss AJ, Klein HU, Zareba W, Goldenberg I, Biton Y, et al. Sustained clinical benefit of cardiac resynchronization therapy in non-LBBB patients with prolonged PR-interval: MADIT-CRT long-term follow-up. *Clin Res Cardiol*. 2016;105(11):944-52.
4. Lin J, Buhr KA, Kipp R. Effect of PR Interval on Outcomes Following Cardiac Resynchronization Therapy: A Secondary Analysis of the COMPANION Trial. *J Cardiovasc Electrophysiol*. 2017;28(2):185-91.



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

Statement

Statement on Antiplatelet Agents and Anticoagulants in Cardiology – 2019

Development: The Department of Clinical Cardiology of the Brazilian Society of Cardiology (Departamento de Cardiologia Clínica da Sociedade Brasileira de Cardiologia)

Norms and Guidelines Council: Fernando Bacal, Leandro Ioschpe Zimerman, Paulo Ricardo Avancini Caramori e Pedro A. Lemos

Norms and Guidelines Coordinator: Ludhmila Abrahão Hajjar

President of the Department of Clinical Cardiology: João Luiz Fernandes Petriz

Statement Coordinator: Carlos V. Serrano Jr.

Statement Authors: Carlos V. Serrano Jr.,^{1,2,3} Alexandre de M. Soeiro,^{1,3} Tatiana C. A. Torres Leal,¹ Lucas C. Godoy,¹ Bruno Biselli,¹ Luiz Akira Hata,¹ Eduardo B. Martins,¹ Isabela C. K. Abud-Manta,^{1,2} Caio A. M. Tavares,¹ Francisco Akira Malta Cardozo,^{1,3} Múcio Tavares de Oliveira Jr.¹

Instituto do Coração do Hospital das Clínicas da Universidade de São Paulo,¹ São Paulo, SP – Brazil

Hospital Israelita Albert Einstein,² São Paulo, SP – Brazil

Hospital Beneficência Portuguesa Mirante,³ São Paulo, SP – Brazil

This statement shall be referred to as:

Serrano Jr. CV, Soeiro AM, Leal TCAT, Godoy LC, Biselli B, Hata LA et al. Statement on Antiplatelet Agents and Anticoagulants in Cardiology – 2019. Arq Bras Cardiol. 2019; 113(1):111-134.

Note: These Guidelines are for information purposes and are not to replace the clinical judgment of a physician, who must ultimately determine the appropriate treatment for each patient.

Correspondence:

Sociedade Brasileira de Cardiologia - Av. Marechal Câmara, 360/330 - Centro - Rio de Janeiro – Postal Code: 20020-907.

E-mail: sbc@cardiol.br.

Declaration of potential conflict of interest of authors/collaborators of the Statement on Antiplatelet Agents and Anticoagulants in Cardiology – 2019

If the last three years the author/developer of the Statement:

Names Members of the Statement	Participated in clinical studies and/or experimental trials supported by pharmaceutical or equipment related to the guideline in question	Has spoken at events or activities sponsored by industry related to the guideline in question	It was (is) advisory board member or director of a pharmaceutical or equipment	Committees participated in completion of research sponsored by industry	Personal or institutional aid received from industry	Produced scientific papers in journals sponsored by industry	It shares the industry
Alexandre de Matos Soeiro	No	Servier, Daiichi Sankyo	No	No	Sanofi	No	No
Bruno Biselli	No	No	No	No	No	No	No
Caio de Assis Moura Tavares	No	No	No	No	No	No	No
Carlos Vicente Serrano Júnior	No	No	No	No	No	No	No
Eduardo Bello Martins	No	No	No	No	No	No	No
Francisco Akira Malta Cardozo	No	No	No	No	No	No	No
Isabela C. K. Abud-Manta	No	No	No	No	No	No	No
Lucas Colombo Godoy	No	No	No	No	No	No	No
Luiz Akira Hata	No	No	No	No	No	No	No
Múcio Tavares de Oliveira Júnior	No	Boehringer Ingelheim, EMS	Sanofi Aventis, Boehringer Ingelheim, Roche Diagnostica, Philips Healthcare, Torrent Pharma	Torrent Pharma	Boehringer Ingelheim, Merck	EMS, Novartis, Torrent Pharma	No
Tatiana C. A. Torres Leal	No	No	No	No	No	No	No

Statement

Content

1. Introduction	113
2. Antithrombotic Therapy in Patients Using Oral Anticoagulants and Undergoing Percutaneous Coronary Intervention	113
2.1. Introduction	113
2.2. Management of Antithrombotic Agents and the Moment of Percutaneous Coronary Intervention	114
2.3. Choosing Stent Type for Percutaneous Coronary Intervention	115
2.4. Long-term Antithrombotic Therapy following Percutaneous Coronary Intervention	115
3. Duration Of Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention	116
3.1. Introduction	116
3.2. Risk Scores	117
3.3. Dual Antiplatelet Therapy Duration following Percutaneous Coronary Intervention for Stable Coronary Artery Disease	119
3.4. Dual Antiplatelet Therapy Duration following Percutaneous Coronary Intervention for Acute Coronary Artery Disease	119
4. Reversal of New Anticoagulants	120
4.1. Introduction	120
4.2. Antidotes	120
4.3. Idarucizumab	121
4.3.1. Andexanet Alfa	121
4.4. Alternative Therapies	121
5. Pericardioversion Anticoagulation in Atrial Fibrillation	122
5.1. Introduction	122
5.2. Strategies for Pericardioversion Anticoagulation in Atrial Fibrillation	122
6. Anticoagulation and Antiplatelet Therapy in Patients with Patent Foramen Ovale	124
6.1. Introduction	124
6.2. Relation between Patent Foramen Ovale and Cryptogenic Stroke	124
6.3. Evidence for the Use of Antiplatelet Agents or Anticoagulants in Patients with Patent Foramen Ovale	125
7. Antithrombotic Therapy in Oncology Patients with Thrombocytopenia	127
7.1. Introduction	127
7.2. Antithrombotic Therapy	127
References	127

1. Introduction

In 2013, the Brazilian Cardiology Society published the “Brazilian Guidelines on Antiplatelet and Anticoagulant Agents in Cardiology.” Over the past years, new studies have been carried out, providing important information on the use of these medications, administered alone and in combination with other medications. It is, therefore, time to review our guidelines and update them with this new knowledge which has been produced.

We have carried out an extensive review of the literature, and for this update we have chosen to emphasize 6 major topics in clinical practice which have undergone innovation over the past years or which were not covered in the previous document. The themes of this update are:

1. Antithrombotic therapy in patients using oral anticoagulants and undergoing percutaneous coronary intervention (PCI);
2. Duration of dual antiplatelet therapy following PCI;
3. Reversal of new anticoagulants;
4. Pericardioversion anticoagulation in atrial fibrillation (AF);
5. Anticoagulation and antiplatelet therapy in patients with patent foramen ovale;
6. Antithrombotic therapy in oncology patients with thrombocytopenia.

In this update, grade of recommendations and level of evidence were applied in accordance with the following standards.

It is our hope that this document may be of benefit to all professionals who, in their daily practice, face dilemmas and doubts regarding the best manner to prescribe various options and doses of available anticoagulants and antiplatelet agents.

Grade of recommendation	
Grade I	Conditions for which there is conclusive evidence or, in the absence of conclusive evidence, general consensus that the procedure is safe and useful/effective
Grade IIa	Conditions for which there are conflicting evidence and/or divergent opinions regarding the procedure's safety and usefulness/effectiveness. Weight or evidence/opinion in favor of the procedure. The majority of studies/experts approve.
Grade IIb	Conditions for which there are conflicting evidence and/or divergent opinions regarding the procedure's safety and usefulness/effectiveness. Safety and usefulness/effectiveness less well established, with no prevailing opinions in favor.
Grade III	Conditions for which there is evidence and/or consensus that the procedure is not useful/effective and may, in some cases, be potentially harmful
Level of evidence	
Level A	Data obtained from multiple concordant large randomized trials and/or robust meta-analysis of randomized clinical trials
Level B	Data obtained from less robust meta-analysis, from a single randomized trial, or from non-randomized (observational) trials
Level C	Data obtained through consensus of expert opinion

2. Antithrombotic Therapy in Patients Using Oral Anticoagulants and Undergoing Percutaneous Coronary Intervention

2.1. Introduction

Approximately 6% to 8% of patients undergoing PCI have a concomitant indication for long-term oral anticoagulant use, owing to various reasons such as AF, mechanical valves, or thromboembolism.¹⁻⁴ It is, thus, fundamental to define the best way to treat these patients, especially regarding the combination of antiplatelet and anticoagulant medications.

For all patients who are receiving oral anticoagulants and who will undergo PCI, it is necessary to proceed to evaluating the need for maintaining anticoagulation and to calculate the risk of bleeding.

When AF is the reason for anticoagulation, the CHA₂DS₂-VASc score should be utilized, and maintenance should only be indicated when the score is ≥ 1 in men or ≥ 2 in women (Table 1). On the other hand, in patients with thromboembolic events or mechanical valve prostheses, anticoagulation should be maintained, regardless of any assessment.⁵⁻⁷

Risk of bleeding should be assessed through the HAS-BLED score (Table 2). When it is ≥ 3 , the patient is classified as at a high risk of bleeding. This should not contraindicate any form of treatment; however, it must be clear that the individual should be accompanied with more frequent consultations and that it is necessary to attempt to modify the risk factors present in the score in order to reduce the risk.⁶⁻⁸

2.2. Management of Antithrombotic Agents and the Moment of Percutaneous Coronary Intervention

Interrupting oral anticoagulation (OAC) during the periprocedural period can increase both the rate of bleeding and the rate of thromboembolic events.

Although there is no consistent evidence, the introduction of parenteral anticoagulants in patients receiving warfarin should only be considered when the international normalized ratio (INR) is less than 2.5. PCI may be performed while using anticoagulants; however, it should be postponed, if possible, until the patient's INR is < 1.5 , unless there is an emergency situation, and it is necessary to take high ischemia risk (GRACE score > 140 , TIMI score ≥ 5 , recurrent angina, refractory angina, hemodynamic instability, or ventricular arrhythmias) into consideration.^{7,8}

Furthermore, for patients receiving new oral anticoagulants (NOAC), there is also no evidence as to whether parenteral

Table 1 – CHA₂DS₂ VASc Criteria

	Description	Points
C	Congestive heart failure	1
H	Hypertension	1
A ₂	Age (≥ 75)	2
D	Diabetes mellitus	1
S ₂	Prior TIA or stroke	2
V	Vascular disease (prior AMI, PAD, or aortic plaque)	1
A	Age (65-74)	1
Sc	Sex (female)	1

AMI: acute myocardial infarction; PAD: peripheral arterial disease; TIA: transient ischemic attack.

Table 2 – HAS-BLED Criteria

	Risk factor	Points
H	Arterial hypertension (SAP > 160 mmHg)	1
A	Abnormal kidney function: CrCl ≤ 50 mL/min or creatinine ≥ 2.26 mg/dL or hemodialysis or kidney transplant	1
	Abnormal liver function: bilirubin $\geq 2 \times$ ULN or AST/ALT/AP $\geq 3 \times$ ULN or hepatic cirrhosis	1
S	Prior stroke	1
B	Prior bleeding or predisposition to bleeding	1
L	Labile INR or $< 60\%$ time within therapeutic range	1
E	Age > 65	1
D	Drug use (NSAID, antiplatelet)	1
	Alcohol use (> 20 U per week)	1

ALT: alanine aminotransferase; AP: alkaline phosphatase; AST: aspartate aminotransferase; CrCl: creatinine clearance; INR: international normalized ratio; NSAID: nonsteroidal anti-inflammatory drugs; SAP: systolic arterial pressure; U: units; ULN: upper limit of normal.

Statement

anticoagulation or PCI should be performed early or not. Once more, when the risk of ischemia is very high, PCI should be performed early, while still under the effect of the medication. The procedure should be postponed, however, whenever the risk of ischemia permits. For patients with creatinine clearance > 50 mL/min, the full effect of NOAC may be considered reversed 24 hours after the last dose. For patients with creatinine clearance, on the other hand, between 30 and 50 mL/min, 48 hours are necessary. Following this period, the patient may thus theoretically undergo PCI with a lower risk of bleeding. Parenteral anticoagulation may be performed in the event that PCI is early, regardless of when the last dose of NOAC was administered.^{7,8}

In all OAC patients, priority vascular access should always be radial, and femoral access should only be performed in exceptional cases.

The use of pre-PCI dual antiplatelet therapy should be routinely avoided in this group of patients. Clopidogrel should only be used once coronary anatomy has been defined and coronary angioplasty with stent placement has been indicated. The use of prasugrel or ticagrelor is contraindicated in this situation, as there is insufficient evidence for their safety in this context. Acetylsalicylic acid (ASA) should always be used at a minimum dose, preferably less than 100 mg daily.^{7,8}

The use of proton pump inhibitors as prophylaxis against stress ulcers in this group of patients should be the first choice considered due to the elevated risk of gastrointestinal bleeding.^{7,8}

2.3. Choosing Stent Type for Percutaneous Coronary Intervention

The choice of stent type (between the newest generation of drug-eluting stents and conventional stents) in patients who require full anticoagulation continues to generate discussion.

Results of the Dual Antiplatelet Therapy (DAPT) study (see section 2.2) showed that the benefits of prolonged dual antiplatelet therapy do not depend on the type of stent used and that the risk of coronary events in patients who suspend therapy due to the need for non-cardiac surgery was the same with either drug-eluting or conventional stents.⁹⁻¹¹

Furthermore, two randomized studies have demonstrated that second-generation drug-eluting stents are superior to conventional stents in patients with high bleeding risks who were not able to tolerate the use of prolonged dual antiplatelet therapy.^{12,13}

In this manner, stent choice should be individualized based on coronary anatomy and bleeding risk. There are, however, no reasons to contraindicate the use of drug-eluting stents in this group of patients.

2.4. Long-term Antithrombotic Therapy following Percutaneous Coronary Intervention

The first instances of evidence on this topic have begun to be published during the last five years, which means that the subject continues to be controversial and to produce doubts.

In 2012, data from the DANISH registry in patients with AF and acute myocardial infarction (AMI) showed that the 90-day

risk of bleeding significantly increased with the use of triple therapy in comparison with anticoagulation combined with only one antiplatelet agent (hazard ratio [HR] = 1.47, 95% CI 1.04 to 2.08) with no differences in ischemic event rates (HR = 1.15, 95% CI 0.95 to 1.40). In this manner, analysis of this observational study would not recommend routine use of triple therapy.^{14,15}

The What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting (WOEST) study, with 573 patients, was the first randomized prospective study published on this topic. All patients were indicated for OAC (69% for AF) and PCI. Patients were divided into 2 groups: warfarin and clopidogrel; and warfarin, clopidogrel, and ASA 80 mg daily. This treatment regimen was maintained for 30 days for conventional stents and 12 months for drug-eluting stents. The primary outcome was any bleeding episode according to TIMI criteria. After 1 one year, they observed a significant reduction in bleeding in the dual therapy group (19.5% versus 44.9%; HR = 0.36, 95% CI 0.26 to 0.50, $p < 0.001$). There was no difference in rates of major bleeding, AMI, stent thrombosis, or stroke. Lower mortality, however, was observed in the dual therapy group (2.5% versus 6.4%, $p = 0.027$).¹⁶

In 2015, the Triple Therapy in Patients on Oral Anticoagulation after Drug Eluting Stent Implantation (ISAR-TRIPLE) multicenter randomized study, with 614 patients, conducted in Germany and Denmark, evaluated whether shortening the duration of clopidogrel therapy from 6 months to 6 weeks after drug-eluting stent implantation would be associated with superior net clinical outcome in patients receiving aspirin and warfarin concomitantly. They included patients who had been receiving oral anticoagulants for AF for at least 12 months and who had received a drug-eluting stent for stable angina or acute coronary syndrome (ACS). The primary outcomes were death, AMI, stent thrombosis, stroke, and major bleeding in 9 months. No differences were observed in relation to the primary outcomes between the 2 groups (9.8% versus 8.8%; HR = 1.14, 95% CI 0.68 to 1.91; $p = 0.63$). On the other hand, the incidence of minor bleeding events was higher in the group that used clopidogrel for 6 months (10.9% versus 7.3%, $p = 0.03$).¹⁷

With respect to NOAC, the PIONEER AF-PCI randomized prospective study evaluated the best pharmacological treatment strategy using rivaroxaban in patients who required OAC due to AF and who were undergoing PCI. The study included 2,124 patients, divided into 3 groups: rivaroxaban (15 mg) + P2Y₁₂ inhibitor for 12 months; rivaroxaban (2.5 mg twice daily) + ASA + P2Y₁₂ inhibitor for 1, 6, and 12 months; and warfarin + ASA + P2Y₁₂ inhibitor for 1, 6, and 12 months. Approximately 93% of patients used clopidogrel as the antiplatelet of choice, and 65% received drug-eluting stent implantation. Approximately 50% of cases had ACS. The primary outcome evaluated was clinically relevant bleeding according to TIMI criteria. They observed bleeding rates of 16.8%, 18.0%, and 26.7%, respectively between the groups ($p < 0.001$). The rates of mortality, stroke, and cardiovascular events did not show any significant differences. For patients with AF who need stent angioplasty, the authors concluded that dual therapy or triple therapy strategies with reduced doses of

rivaroxaban were safer and that they reduced bleeding rates in comparison with conventional triple therapy.¹⁸

Similarly, in 2017, the Evaluation of Dual Therapy with Dabigatran vs. Triple Therapy with Warfarin in Patients with AF that Undergo a PCI with Stenting (REDUAL-PCI) multicenter randomized prospective study included 2,725 patients with AF who underwent PCI, divided into triple therapy (warfarin + clopidogrel/ticagrelor + ASA) versus dabigatran + clopidogrel/ticagrelor. The primary outcome was major or clinically relevant bleeding. Furthermore, they tested the noninferiority of dual therapy in relation to thromboembolic events, death, and revascularization. The bleeding rate was 15.4% in the group that received 110 mg of dabigatran compared to 26.9% in the triple therapy group ($p < 0.001$ for noninferiority). In patients who received 150 mg of dabigatran, the bleeding rate was 20.2% compared to 25.7% in the triple therapy group ($p < 0.001$ for noninferiority). The combined events rates were 13.7% and 13.4% in the double and triple therapy groups, respectively ($p = 0.005$ for noninferiority). They mainly observed a reduced need for revascularization. The use of dual therapy with dabigatran was thus shown to be noninferior to triple therapy. As in the PIONEER AF-PCI study, the REDUAL-PCI study was not powered to show differences in coronary events or death. It was only possible to evaluate safety.¹⁹

Triple therapy should, thus, be considered only for patients with low hemorrhage risks during the shortest time possible (preferably 1 month, with the possibility of extending up to 6 months). After this period, anticoagulant use combined with just 1 antiplatelet agent should be maintained. However, when there is a high ischemia risk (Table 3) as well as a high hemorrhage risk, the recommendation is to use triple therapy for, at most, 1 month or to initiate dual therapy with an anticoagulant and clopidogrel directly (Table 4 and Figure 1).

On the other hand, in patients with high risks of bleeding and low ischemia risks, in accordance with the results of the main published studies, the current recommendation is to initiate dual therapy with an anticoagulant and clopidogrel from the beginning (Table 4 and Figure 1).

It is, preferably, recommended to use NOAC instead of warfarin, due to the predictability of their effect. Furthermore, the NOAC should be chosen in accordance with the medical knowledge already established in this context and at doses

previously studied in scientific research. When opting to use warfarin, the INR should be maintained close to 2.0.

Suspension of the antiplatelet agent is recommended 12 months after the last coronary event. Evidence for this conduct is scarce; it is, however, based on studies that showed that, after 1 year, anticoagulation is superior to ASA and that the combination, in addition to increasing bleeding rate, has no additional benefits.²⁰ Combined therapy with clopidogrel and OAC may be prolonged for more than 1 year in patients with high ischemia risk and mechanical valve prostheses.

3. Duration of Dual Antiplatelet Therapy Following Percutaneous Coronary Intervention

3.1. Introduction

The combination of P2Y₁₂ inhibitors with ASA monotherapy is known to be a great ally in the management of patients with coronary artery disease (CAD), be it acute or stable, and it reduces the risk of atherothrombotic phenomena, as well as stent thrombosis rates following PCI.²¹⁻²³ This reduced ischemia risk is, however, indisputably associated with higher bleeding rates.²²⁻²⁵

The state of the art is to weigh the risks and benefits of dual therapy, as well as treatment duration, by contemplating clinical characteristics, the anatomical characteristics of the lesions addressed, and the type of stent used.

The risk of stent thrombosis in patients who have undergone PCI with conventional (metallic) stents is much more frequent during the first days and weeks following the procedure. In this manner, dual antiplatelet therapy is recommended for 1 month.²⁶ With the advent of drug-eluting stents, conventional stents have been reserved, ideally, for patients with very high risks of bleeding who need shorter periods (at least 1 month) of dual antiplatelet therapy. In Brazil, however, conventional metallic stents continue to be used, especially in public health services.

Thrombosis in first-generation drug-eluting stents intensified perspectives on therapy duration in the past.²⁷ Although the relative risk is still considerable, late or very late

Table 3 – Definition of high long-term ischemic risk

Prior history of stent thrombosis during adequate antiplatelet therapy
"Final" artery angioplasty
Multiarterial coronary disease, especially in patients with diabetes
Chronic renal insufficiency (CrCl < 60 mL/min)
At least 3 stents and/or 3 lesions treated
PCI in bifurcation, with at least 2 stents placed
Total stent length > 60 mm
Treatment for chronic coronary occlusion

CrCl: creatinine clearance.

Statement

Table 4 – Recommendation for managing patients who require oral anticoagulation undergoing percutaneous coronary intervention

Indications	Grade of recommendation	Level of evidence
The CHA ₂ DS ₂ -VASc score should be used to evaluate the need for maintaining anticoagulation, and the HAS-BLED score should be used to calculate the risk of bleeding	Ila	C
During PCI, priority vascular access should always be radial, and femoral access should only be performed in exceptional cases.	Ila	C
Triple therapy should be considered for the shortest time possible, due to the high associated risk of hemorrhage.	Ila	C
Utilization of NOAC should be given preference over warfarin, due to the predictability of their effect.	Ila	C
When opting to use warfarin, INR should be maintained close to 2.0.	Ila	C
Clopidogrel should only be used once coronary anatomy has been defined and coronary angioplasty with stent placement has been indicated, and routine pre-PCI administration should be avoided.	Ila	C
The use of prasugrel or ticagrelor is contraindicated in this situation.	III	C
ASA should always be used at a minimum dose, preferably ≤ 100 mg daily.	Ila	C
The use of proton pump inhibitors as prophylaxis against stress ulcers in this group of patients should be the first choice considered, due to the elevated risk of gastrointestinal bleeding.	Ila	C
Triple therapy should be considered for patients with low hemorrhage risks during the shortest time possible (preferably 1 month, with the possibility of extending up to 6 months). After this period, anticoagulant use in combination with just one antiplatelet agent should be maintained.	Ila	B
When there is a high ischemia risk as well as a high hemorrhage risk, the recommendation is to use triple therapy for, at most, 1 month or to begin dual therapy with an anticoagulant and clopidogrel directly.	Ila	B
In patients with high risks of bleeding and low ischemia risks, dual therapy with an anticoagulant and clopidogrel should be initiated from the beginning.	Ila	A
When opting to use NOAC, the combination of dual therapy with clopidogrel 75 mg daily and rivaroxaban 15 mg daily or dabigatran 110 mg twice daily should be the first choice.	IIb	B
Discontinuation of antiplatelet therapy should be considered after 12 months.	Ila	B

ASA: acetylsalicylic acid; INR: international normalized ratio; NOAC: new oral anticoagulant; PCI: percutaneous coronary intervention.

thrombosis in second-, third-, and fourth-generation drug-eluting stents has considerably reduced with modernization of the drugs eluted and the materials utilized. This has, thus, made it possible for dual therapy duration to be as short as possible, seeing that the risk of bleeding does not justify the small absolute benefit of reducing very late thrombosis. The use of first-generation drug-eluting stents is already infrequent in Brazil. For this reason, these guidelines do not include a discussion of treatment duration following percutaneous implantation of this type of stent.

The use of bioresorbable stents is already a reality in some centers. There are no studies to determine the ideal dual antiplatelet therapy duration specifically for this type of stent, although the recommendation for treatment duration is approximately 12 months. Some meta-analyses have suggested a lower rate of thrombosis in this type of stent in comparison with drug-eluting stents during the first 30 days following implantation. Use of the most potent P2Y₁₂ inhibitors is thus indicated for this patient profile. There is still an increased risk of very late thrombosis, and longer treatment (more than 12 months) may consequently be considered for patients with low bleeding risks. Specific studies, however, are still lacking to reinforce this recommendation.²⁸⁻³¹

3.2. Risk Scores

There are several known risk factors related to higher risks of ischemic events and bleeding episodes. Some of these factors are also related to both situations, which makes the medical decision even more complex.

Internationally implemented risk scores are currently available to aid in weighing treatment extension, taking the risk of bleeding and the benefit of reduced atherothrombotic risk into consideration.^{32,33} Based on studies, 2 scores have been elaborated: the DAPT score and the PRECISE-DAPT score.

The DAPT score (Table 5) was developed based on analysis of 11,648 patients included in the Dual Antiplatelet Therapy Study (DAPT) trial, and it has been validated in 8,136 patients who participated in the Patient Related Outcomes with Endeavor vs. Cypher Stenting (PROTECT) trial. Nine factors were identified: age, heart failure (HF) or reduced left ventricular ejection fraction (LVEF), saphenous vein graft stent implantation, AMI at initial presentation, prior AMI or prior PCI, paclitaxel-eluting stent, diabetes, stent diameter < 3 mm, and current tobacco use, resulting in a sum of points varying from -2 to +10. Patients with high DAPT scores (≥ 2) receive more benefits from prolonged dual antiplatelet therapy, as evaluated in cited study, over an average period of

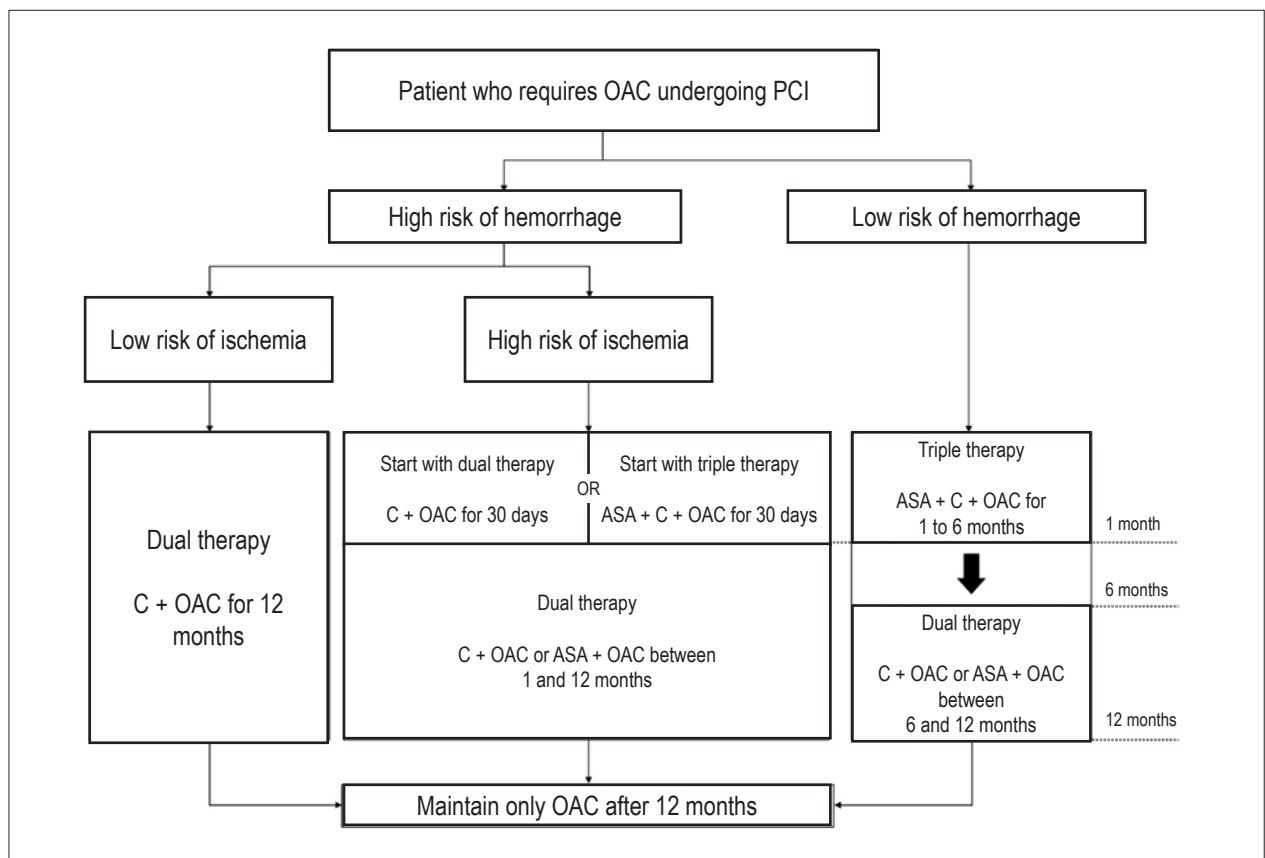


Figure 1 – Flowchart representing indications for antithrombotic therapy combinations in accordance with ischemic and hemorrhagic risk. C: clopidogrel; OAC: oral anticoagulant; PCI: percutaneous coronary intervention.

30 months, given the reduction in AMI, stent thrombosis, and cardiovascular and cerebrovascular events, at the expense of a small increase in the risk of bleeding (NNT = 34 versus NNH = 272). On the other hand, patients with low DAPT scores (< 2) have an increased risk of events related to bleeding, with no reduction in the rate of cardiovascular and cerebrovascular events (NNH 64).³²

The Predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) included 14,963 patients undergoing elective, urgent, or emergency PCI, randomized into long (12 to 24 months) or short (3 to 6 months) dual antiplatelet therapy durations, with relation to bleeding risk based on 5 factors: age, creatinine clearance, hemoglobin, white-blood-cell count, or prior spontaneous bleeding (calculator available at www.precisedaptscore.com). In patients with high PRECISE-DAPT scores (≥ 25), prolonged therapy was associated with higher bleeding rates and no ischemic benefits; in contrast, patients with low PRECISE-DAPT scores had low combined adverse ischemic events with no significant increase in risk of bleeding.³³

Table 5 – Factors used to calculate DAPT score. Scores ≥ 2 are associated with favorable risk-benefit, whereas scores < 2 are associated with unfavorable risk-benefit

Age ≥ 75	Points
Age > 65 and < 75	-2
Age < 65	-1
Current tobacco use	0
Diabetes mellitus	1
AMI at initial presentation	1
Prior PCI or AMI	1
Stent diameter < 3 mm	1
Paclitaxel-eluting stent	1
HF or reduced LVEF	1
Saphenous vein graft PCI	2
ICP em enxerto de veia safena	2

AMI: acute myocardial infarction; HF: heart failure; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention.

Statement

Scientific evidence tested in randomized studies is lacking to evaluate the real value of these scores in improving long-term outcomes for patients receiving dual antiplatelet therapy and undergoing PCI. Nevertheless, their utilization may be considered when individualizing decisions and contemplating the risks and benefits of prolonging dual antiplatelet therapy.

3.3. Dual Antiplatelet Therapy Duration following Percutaneous Coronary Intervention for Stable Coronary Artery Disease

Dual antiplatelet therapy in stable cases of CAD is not routinely indicated for patients receiving clinical treatment. It is only effectively necessary to indicate this following PCI, and the combination of ASA and clopidogrel is preferable.

There is no evidence from randomized studies on the use of prasugrel and ticagrelor as an option over clopidogrel for this patient profile. They are, however, options which may be considered for patients with high atherothrombotic risks if there is evidence that clopidogrel is not effective based on previous clinical outcomes or for patients who receive implantation of a bioresorbable stent.

Of the studies that evaluate dual antiplatelet therapy duration (ASA and clopidogrel) in stable patients, 3 are more recent, and they compare 6 months with 12 to 24 months of treatment. The Safety and Efficacy of 6 Months Dual Antiplatelet Therapy after Drug Eluting Stenting (ISAR-SAFE) study,³⁴ which was the largest, randomized 4,005 patients and confirmed that there are no benefits and no reduction in ischemic events with the use of dual antiplatelet therapy for 12 months in comparison with 6 months. Similar results were also found in the Is There a Life for DES after Discontinuation of Clopidogrel? (ITALIC)³⁵ and Second Generation Drug-eluting Stent Implantation followed by Six- versus Twelve-month Dual Antiplatelet Therapy (SECURITY) studies.³⁶

Other meta-analyses^{37,38} have shown that 12 months of therapy did not add benefits in relation to reduced

ischemic events in comparison with shorter therapy duration (< 6 months, including evaluation of studies that analyzed 3 months of therapy), which may be an option for patients with lower bleeding risks.

The DAPT trial and other meta-analyses³⁷⁻³⁹ have demonstrated that, in addition to reduced ischemic events, stent thrombosis, and infarction rates, as well as increased bleeding rates, therapy prolonged for more than 12 months showed a possible, albeit weak, relation to increased general mortality.

The recommendation of these guidelines is, thus, based on average dual antiplatelet therapy duration of 6 months following PCI in stable patients, with the possibility of considering a period of 3 months for patients with high bleeding risks. More prolonged use (> 12 months) is not routinely indicated and may be considered in accordance with the patient's clinical and anatomical profile (Table 6).

3.4. Dual Antiplatelet Therapy Duration following Percutaneous Coronary Intervention for Acute Coronary Artery Disease

Ticagrelor and prasugrel are preferential P2Y₁₂ inhibitors for patients undergoing PCI after ACS.

In patients who have ACS, the ischemia risk continues to be higher until approximately 1 year after the event, even after the culprit and non-culprit lesions have been treated.^{22,20,40,41} The main studies which affirm that ticagrelor and prasugrel have benefits over clopidogrel consider a reduction in events with an average treatment duration of 12 months.

A meta-analysis of 3 studies which compared 3, 6, and 12 months of dual therapy, including 11,473 patients, 4,758 of which had ACS, demonstrated that dual antiplatelet therapy for ≤ 6 months was associated with an increased risk of infarction, which was, however, not statistically significant. Considering the lower number of acute patients in comparison with studies that demonstrated the real benefits of intense dual antiplatelet therapy with ticagrelor and prasugrel (TRITON

Table 6 – Recommendations on duration of dual antiplatelet therapy following percutaneous coronary intervention in stable coronary artery disease

Indications	Grade of recommendation	Level of evidence
In patients with stable CAD undergoing PCI who need dual antiplatelet therapy, the preferred combination is clopidogrel (75 mg) and a dose of ASA (75 to 200 mg)	I	A
The use of drug-eluting stents is always preferable to conventional stents, regardless of dual antiplatelet therapy duration	I	A
In patients with stable CAD undergoing PCI with a drug-eluting stent, dual antiplatelet therapy should be maintained for a minimum period of 6 months, regardless of stent type	I	A
In patients with stable CAD undergoing PCI with a conventional stent, dual antiplatelet therapy may be maintained for a minimum period of 1 month when there is a high risk of bleeding	I	A
In patients with stable CAD undergoing PCI with a drug-eluting stent who have high bleeding risks, the suspension of dual antiplatelet therapy may be considered	IIa	B
In patients with stable CAD undergoing PCI with a drug-eluting stent who tolerate the routine dual antiplatelet therapy duration without bleeding episodes and who have low bleeding risks and high atherothrombotic risks (DAPT score ≥ 2 and PRECISE-DAPT < 25), it is possible to maintain antiplatelet therapy for > 12 months and ≤ 30 months	IIb	A

ASA: acetylsalicylic acid; CAD: coronary artery disease; PCI: percutaneous coronary intervention.

and PLATO), the discontinuation of dual antiplatelet therapy may be considered in patients with increased bleeding risks as early as 6 months after treatment initiation.⁴²

The PEGASUS study evaluated patients who had had infarction 1 to 3 years prior to randomization. They studied the standard dose of ticagrelor (90 mg every 12 hours), a lower dose of ticagrelor (60 mg every 12 hours) and placebo. All patients received ASA and were followed for a median of 33 months. There was a significant reduction in the rates of infarction, cardiovascular death, and stroke, at the expense of an increase in events related to bleeding. The 60-mg dose of ticagrelor, however, demonstrated lower rates of bleeding in comparison with the 90-mg dose.⁴³

In following with this, the recommendation of these guidelines is to administer dual antiplatelet therapy for at least 12 months to patients undergoing PCI after ACS, which may be modified to a minimum duration of 6 months in the event of increased risks of bleeding. In the same manner as in stable coronary disease, more prolonged use (> 12 months) is not routinely indicated and may be considered in accordance with patients' clinical and anatomical profiles. When opting for this more prolonged treatment, a 60-mg dose of ticagrelor every 12 hours may be considered in combination with ASA (Table 7).

4. Reversal of New Anticoagulants

4.1. Introduction

At the same time that NOAC have been considered noninferior to vitamin K antagonists for ischemic stroke prevention in patients with AF and deep venous thrombosis treatment, they are related to lower risks of major bleeding, particularly hemorrhagic stroke.⁴⁴

Furthermore, notwithstanding the current unavailability of antidotes for all NOAC, major bleeding episodes caused by these drugs do not seem to lead to worse clinical outcomes when compared to bleeding episodes in patients receiving vitamin K antagonists whose anticoagulant effects may be rapidly reversed.⁴⁵

With the increased use of NOAC in clinical practice, the management of hemorrhagic events and the need to reverse anticoagulant effects in order to perform urgent procedures in patients receiving these medications have become common in emergency units.

In addition to general measures (Table 8), the utilization of antidotes, alternative therapies (e.g., prothrombin complex concentrates, factor VIIa, tranexamic acid) and the action of specialized teams (e.g., hematologists, endoscopists, neurologists, neurosurgeons, general surgeons, vascular surgeons, etc.) should be part of institutional protocols for reversing anticoagulation in the event of major bleeding episodes or urgent surgical procedures in patients receiving NOAC.⁴⁶

4.2. Antidotes

Three antidotes are in diverse developmental phases (Table 10). To date, only the monoclonal antibody idarucizumab has been approved for commercial use as an antidote for dabigatran. Andexanet alfa, an antidote for factor Xa inhibitors (rivaroxaban, apixaban, and edoxaban), has yet to be approved for commercial use in Brazil. Finally, ciraparantag, which is still in the early stages of development, is potentially capable of neutralizing the effects of both direct thrombin inhibitors and factor Xa inhibitors (Tables 9 and 10).

Potential indications for the use of antidotes for NOAC include:

- A life-threatening bleeding episode (e.g. hemorrhagic stroke) or uncontrollable bleeding;
- Persistent bleeding, notwithstanding hemostatic measures;
- Risk of recurrent bleeding due to NOAC overdose or expected metabolism delay (e.g., renal insufficiency);
- Bleeding in non-compressible locations or in vital organs (e.g., retroperitoneal, pericardial, or intraocular bleeding or intramuscular bleeding with compartment syndrome);

Table 8 – General measures for controlling major bleeding events in patients receiving NOAC

Mechanical compression when possible
Determining last dose of NOAC
Exams (renal and hepatic function, hemogram, complete coagulogram, and factor anti-Xa)
Volume expansion and red cell concentrate, when necessary
Activated charcoal if NOAC was taken < 2 hours prior

NOAC: new oral anticoagulant.

Table 7 – Recommendations on duration of dual antiplatelet therapy following percutaneous coronary intervention in acute coronary syndrome

Indications	Grade of recommendation	Level of evidence
In patients with ACS undergoing PCI, regardless of stent type, dual antiplatelet therapy should be maintained for a minimum period of 12 months	I	A
In patients with ACS undergoing PCI with increased risks of bleeding, it is possible to consider maintaining dual antiplatelet therapy for a minimum period of 6 months	IIa	B
In patients with ACS undergoing PCI with a drug-eluting stent who tolerate the routine dual antiplatelet therapy duration without bleeding episodes and who have low bleeding risks and high atherothrombotic risks (DAPT score ≥ 2 and PRECISE-DAPT < 25), it is possible to maintain antiplatelet therapy for > 12 months and ≤ 30 months	IIb	A

ACS: acute coronary syndrome; PCI: percutaneous coronary intervention.

Statement

Table 9 – Reversal of NOAC anticoagulant effects^a

NOAC	Specific antidote	Alternative therapeutic options
Dabigatran	Idarucizumab 5 g IV (divided in 2 doses of 2.5 g)	• PCC 50 IU/kg IV • rFVIIa 90 mcg/kg IV every 2 hours • Tranexamic acid 15 to 30 mg/kg IV • Hemodialysis
Rivaroxaban	Anti-factor Xa (e.g., Andexanet alfa – not approved)	• PCC 50 IU/kg IV • rFVIIa 90 mcg/kg IV every 2 hours • Tranexamic acid 15 to 30 mg/kg IV
Apixaban	Anti-factor Xa (e.g., Andexanet alfa – not approved)	• PCC 50 IU/kg IV • rFVIIa 90 mcg/kg IV every 2 hours • Tranexamic acid 15 to 30 mg/kg IV
Edoxaban	Anti-factor Xa (e.g., Andexanet alfa – not approved)	• PCC 50 IU/kg IV • rFVIIa 90 mcg/kg IV every 2 hours • Tranexamic acid 15 to 30mg/kg IV

IV: intravenous; NOAC: new oral anticoagulant; PCC: prothrombin complex concentrates; rFVIIa: recombinant activated factor VII.

Table 10 – Recommendations on the use of NOAC antidotes

Indications	Grade of recommendation	Level of evidence
The use of idarucizumab in patients receiving dabigatran is indicated at a dose of 5 g intravenous, when emergency intervention or surgery are necessary in patients who cannot wait the time it takes to metabolize the anticoagulant or in the event of life-threatening or uncontrollable bleeding episodes	Ila	B
In the event of surgeries or procedures which are elective or for which it is possible to wait the NOAC clearance time, controlled bleeding events, or anticoagulant overdoses without bleeding, the use of antidotes should not be indicated	III	C

NOAC: new oral anticoagulant.

- Need for emergency surgical intervention in patients with high risks of bleeding who cannot wait the time it takes to metabolize NOAC.

The use of antidotes does not seem to be necessary in patients who have received the last dose of NOAC more than 24 hours prior and who have creatinine clearance > 60 mL/min. In the event of elective surgeries or procedures, patients who may wait the time it takes to metabolize the NOAC, controlled bleeding, or anticoagulant overdose with no bleeding, antidote use does not need to be indicated.⁴⁷

4.3. Idarucizumab

Idarucizumab is a monoclonal antibody fragment that neutralizes the anticoagulant effect of dabigatran by direct binding. Dabigatran, idarucizumab, and dabigatran-idarucizumab are eliminated by the kidneys.

The phase III Reversal Effects of Idarucizumab on Active Dabigatran (REVERSE-AD) study has shown that the intravenous use of 5 g of idarucizumab (2 consecutive doses of 2.5 g at 15-minute intervals) reverted the anticoagulant effect of dabigatran with normalization of thrombin time in more than 98% of patients, leading to early hemostasis in patients with major bleedings and low rates of hemorrhagic events in patients undergoing urgent surgery.⁴⁸

4.3.1. Andexanet alfa

Andexanet alfa is a recombinant factor Xa protein that binds to direct and indirect factor Xa inhibitors, removing them from circulation.

Phase II studies in healthy elderly patients have demonstrated that this drug, administered via intravenous bolus with subsequent continuous 2-hour infusion, reverted more than 90% of rivaroxaban and apixaban's anti-Xa factor activity.⁴⁹ The phase III Ability of Andexanet Alfa to Reverse the Anticoagulant Activity-4 study, which is currently underway, will evaluate the efficacy and safety of andexanet in controlling hemostasis in patients receiving rivaroxaban, apixaban, and edoxaban who have major bleedings. Interim analysis of the study with 67 patients showed a reduction in anti-Xa factor activity in 89% and 93% of patients using rivaroxaban and apixaban, with 70% clinical hemostasis.⁵⁰

4.4. Alternative Therapies

Fresh frozen plasma (FFP), prothrombin complex concentrates (PCC), recombinant activated factor VII, and tranexamic acid are suggested as alternative therapies for patients receiving NOAC who have life-threatening hemorrhagic events or who need to undergo urgent procedures in the absence of a specific antidote (Table 9).⁴⁶

Animal model, in vitro, and case series studies have demonstrated improved laboratory parameters for coagulation in patients receiving rivaroxaban.⁵¹⁻⁵³ On the other hand, new evidence has suggested the superiority of recombinant activated factor VII and partially activated prothrombin complex concentrate (FEIBA) in relation to PCC in patients receiving rivaroxaban.^{54,55} A randomized placebo-controlled study in healthy individuals receiving dabigatran failed to show benefits of PCC use in improving laboratory parameters of coagulation.⁵⁶ Furthermore, case series studies have shown controversial results for the use of FFP, PCC, recombinant activated factor VII, and fibrinogen.⁵⁷

The absence of evidence on clinical reversal of anticoagulant effects of NOAC through the utilization of these alternative homeostatic agents, as well as conflicting data in relation to effects and optimal dosages, make routine use of these medications controversial.

Finally, hemodialysis may remove approximately 49% to 57% of circulating dabigatran in up to 4 hours, seeing that only 35% of the drug is bound to plasma proteins. Patients with renal insufficiency and dabigatran overdose may benefit from hemodialysis in the context of major hemorrhagic events or the need for urgent procedures (Table 10). As rivaroxaban and apixaban are highly bound to plasma proteins, they are not removed by hemodialysis.⁴⁶

5. Pericardioversion Anticoagulation in Atrial Fibrillation

5.1. Introduction

AF is the most common sustained arrhythmia in clinical practice. Its incidence and prevalence increase with age, with a prevalence of 8% in the population over age 80.⁵⁸ Furthermore, some American studies have shown that this prevalence increases by about 0.3% per year and that it had an absolute growth of 4.5% between 1997 and 2007.⁵⁸ The reason behind this increase, in addition to population aging, is related to the improvements in treatment of chronic heart diseases, which increases the number of susceptible individuals, in addition to improved diagnostic tools with greater documentation of this arrhythmia.⁵⁹

AF is associated with increased risk of stroke, as well as heart failure and total mortality.⁶⁰⁻⁶⁴ At least 20% of stroke cases are caused by AF, and these cases of stroke are generally more severe and incapacitating than ischemic stroke.⁶⁵⁻⁶⁷ Some studies have also shown increased risks of cognitive impairment secondary to asymptomatic embolic events in this population.⁶⁸

Antithrombotic therapy plays a fundamental role in the prevention of embolic events when these risk factors are present, making it one of the main pillar of treatment, regardless of the strategy adopted (sinus rhythm or heart rate control).^{69,70} Risk may be calculated using the CHA₂DS₂-VASc score⁷¹ (Table 11), with an indication for chronic anticoagulation if the score is greater than or equal to 2 points, as long as there are no contraindications and the bleeding risk is acceptable.

Warfarin is highly effective in preventing thromboembolic phenomena in AF, with a 64% reduction of risk in patients who receive adequate treatment.⁷²⁻⁷⁴ However, at least half of patients do not receive adequate treatment, for reasons that vary from difficulties in frequent INR monitoring to high risks of bleeding.^{72,73} Furthermore, patients receiving warfarin are not always within the appropriate therapeutic range (INR generally between 2 and 3), due to the occurrence of drug interactions (especially with antibiotic and anti-inflammatory drugs), food interactions, irregular medication use, and acute clinical intercurrents, among others.

With new anticoagulants becoming available over the past years, there have been improvements in relation to anticoagulation monitoring, given that they do not require INR monitoring, that they have few interactions with drugs and food, as well as elevated efficacy and safety, thus making it possible to increase treatment adherence and number of patients treated.⁷⁵ The anticoagulants which have already been investigated are dabigatran, rivaroxaban, apixaban, and edoxaban. Dabigatran is a direct thrombin inhibitor, while the other 3 are factor Xa blockers, and they are used in clinical practice for patients with nonvalvular AF.

5.2. Strategies for Pericardioversion Anticoagulation in Atrial Fibrillation

When AF is reversed to sinus rhythm, either spontaneously or intentionally (via chemical or electrical cardioversion), the short-term risk of thromboembolism increases even more, with the majority of events occurring during the first 10 days after rhythm reversal.⁷⁶⁻⁸¹ The group with the highest risk is that of patients with AF lasting more than 48 hours (1% to 5% during the first month, in the absence of anticoagulation).^{82,83}

Embolism is a consequence of thrombus dislocation from the left atrium after the return of synchronous contraction; there may also, however, be thrombus formation after cardioversion, and this is the reason for indicating anticoagulation for at least 4 months following cardioversion, even in low-risk patients.⁸⁴⁻⁸⁶

The risk of thromboembolism may be reduced to 0% to 0.9% with anticoagulation for at least 3 weeks before cardioversion and 1 month after the procedure.⁸⁵⁻⁸⁹ A further option, with less anticoagulation time, is to evaluate the presence of atrial thrombi via transesophageal echocardiography (TEE) and, in the absence of thrombi, proceed to cardioversion, initiating full anticoagulation at the moment of the procedure and maintaining it for at least 4 weeks.

Warfarin is the most studied anticoagulant in this scenario;⁹⁰⁻⁹⁹ there is, however, sufficient evidence to use NOAC when performing the procedure, and NOAC are, moreover, preferable in some cases, for instance, when the patient is already receiving an NOAC, in order to shorten the pericardioversion anticoagulation period (With warfarin, average time to adjust to adequate INR for at least 3 weeks is 6–8 weeks), or when there are difficulties in INR management.

Regarding pericardioversion, rivaroxaban has been compared to vitamin K antagonists in the X-VerT study, which randomized 1,504 patients with AF of more than 48 hours or unknown duration to receive 1 of the 2

Statement

Table 11 – Recommendations on cardioversion anticoagulation in atrial fibrillation

Indications	Grade of recommendation	Level of evidence
Electrical cardioversion is recommended for patients with hemodynamic instability to reestablish cardiac output	I	B
Anticoagulation with heparin or a new oral anticoagulant should be initiated as soon as possible before any cardioversion for AF or flutter	Ila	B
In stable patients, with persistent AF, who are to undergo electrical or chemical cardioversion, OAC is recommended for at least 3 weeks before and 4 weeks after cardioversion within the therapeutic range (INR between 2 and 3). After 4 weeks, OAC maintenance should be in accordance with CHA ₂ DS ₂ -VASc risk score	I	B
TEE is recommended to exclude thrombi as an alternative to periprocedural anticoagulation when early cardioversion is programmed	I	B
In the event that a thrombus is identified, anticoagulation should be maintained for 3 weeks	I	C
It is recommended to repeat TEE after 3 weeks of anticoagulation to ensure that the thrombus has been resolved before cardioversion	Ila	C
During the pericardioversion period, it is possible to opt for OAC with vitamin K antagonists or new anticoagulants, for the previously described duration	Ila	B
The use of OAC is indicated for patients with atrial flutter, with the same considerations as in AF	I	C
The preferred dose of rivaroxaban should be 20 mg daily, as long as there is a low risk of bleeding	I	B
The preferred dose of dabigatran should be 150 mg twice daily, as long as there is a low risk of bleeding	I	B
The preferred dose of apixaban should be 5 mg twice daily, as long as there is a low risk of bleeding	I	B
For patients undergoing electrical cardioversion guided by TEE without thrombi, UFH is recommended EV (bolus following by continuous infusion) before cardioversion and should be maintained until full OAC is reached	I	B
For patients with AF who need emergency electrical cardioversion, UFH is recommended EV (bolus following by continuous infusion)	I	C
For patients undergoing electrical cardioversion guided by TEE without thrombi, LMWH is recommended before cardioversion and should be maintained until full OAC is reached	I	B
For patients with AF who need emergency electrical cardioversion, a full dose of LMWH is recommended	I	C

AF: atrial fibrillation; EV: endovenous; INR: international normalized ratio; LMWH: low-molecular weight heparin; OAC: oral anticoagulation; TEE: transesophageal echocardiography; UFH: unfractionated heparin.

anticoagulants. There were no significant differences in the primary outcome, which was a composite of transient ischemic attack, stroke, peripheral embolism, AMI, and cardiovascular death (0.51% versus 1.02%; risk ratio [RR] 0.5; 95% CI 0.15 to 1.73), or the safety outcome, which was major bleeding (0.6% versus 0.8%; RR 0.76; 95% CI 0.21 to 2.67). Time to cardioversion was shorter in the rivaroxaban group.⁷⁹ Furthermore, post hoc analysis of the ROCKET-AF study also showed no difference in events between patients who underwent cardioversion using rivaroxaban or warfarin (HR 1.38; 95% CI 0.61 to 3.11).¹⁰⁰

With relation to dabigatran, which is a direct thrombin inhibitor, post-hoc analysis of the RE-LY study observed that 1,983 cardioversions were performed with 1,270 patients (from the total of more than 18,000 patients randomized in the original study). The incidence of stroke or systemic embolism in up to 30 days after cardioversion was similar between the groups receiving pericardioversion anticoagulation with warfarin, dabigatran 110 mg twice daily, and dabigatran 150 mg twice daily (0.6%, 0.8%, and 0.3%, respectively; $p > 0.05$). In the same manner, there were no differences in bleeding rates between the groups (0.6%, 1.7%, and 0.6%, respectively; $p > 0.05$). The results were not altered by prior TEE.⁷⁷ Moreover, an observational Danish study, which compared

456 patients with nonvalvular AF receiving dabigatran with 774 patients receiving warfarin, provided evidence that there was a reduced median time to first cardioversion (4.0 weeks, with interquartile interval [IQI] of 2.9 to 6.5 compared to 6.9 weeks, with IQI of 3.9 to 12.1, for dabigatran and warfarin, respectively). No differences were observed between the 2 drugs regarding efficacy and safety.¹⁰¹

With relation to apixaban, post-hoc analysis of the ARISTOTLE study compared patients who underwent cardioversion receiving apixaban or warfarin. A total of 743 cardioversions occurred in 540 patients, with 265 patients in the apixaban group and 275 in the warfarin group. Average age (67 years old) and LVEF (around 52%) were similar in both groups, and average CHADS₂ score in the apixaban group was 1.8 (± 1.0) and 1.9 (± 1.1 ; $p = 0.17$) in the warfarin group. There were no (zero) strokes or embolic events over 30 days in either of the groups, and 1 major bleeding episode occurred in each group.⁷⁸ These data were subsequently confirmed in the EMANATE trial, which was presented at the European Congress of Cardiology in 2017 (to be published). In this study, 1,500 patients were randomized to receive apixaban or heparin/warfarin (conventional treatment) within 48 hours after cardioversion. Average age in both groups was approximately 64, and average CHA₂DS₂-VASc scores were

2.4 in both treatments. No ischemic events were observed in the apixaban group, while 6 events occurred in the conventional treatment group ($p = 0.016$). Finally, edoxaban was evaluated during the pericardioversion period in 2,199 patients in the ENSURE-AF randomized prospective study, in comparison with enoxaparin and warfarin, with enoxaparin being suspended when $\text{INR} > 2$. There were no differences regarding the primary outcome composed of stroke, systemic embolism, myocardial infarction, or cardiovascular death (odds ratio 0.46; 95% CI 0.12 to 1.4) or in the safety outcome of bleeding (odds ratio 1.48; 95% CI 0.64 to 3.55) for a total period of 28 days of treatment, followed up for more than 30 days.⁸⁰

In specific situations, for instance, for patients who are highly symptomatic or patients with high bleeding risks, cardioversion may be performed earlier, without 3 weeks of anticoagulation, as long as there are no thrombi in the atria or atrial appendices evaluated by TEE. Subsequently, anticoagulation is maintained for at least 4 weeks.^{71,102} If TEE indicates that thrombi are present, anticoagulation is maintained for 3 weeks, and, in the event that cardioversion is scheduled, TEE should be repeated before the procedure. If there are doubts regarding medical adherence, TEE is also indicated in order to rule out thrombus.^{78,103}

This strategy was first evaluated in a randomized manner by the ACUTE study, which compared TEE and the conventional strategy (anticoagulation for 3 weeks before cardioversion). Patients randomized to TEE received heparin if they were hospitalized or warfarin for 5 days before TEE if they were not hospitalized, and cardioversion was performed if there were no thrombi. If they had thrombi (12% of patients), cardioversion was postponed for 3 weeks, with anticoagulation maintained during this period. There were no differences between the TEE and conventional groups regarding the incidence of ischemic stroke (0.6% versus 0.3%, respectively, RR 1.95, 95% CI 0.36 to 10.60) or embolic events in general (0.8% versus 0.5%, respectively, RR 1.62, 95% CI 0.39 to 6.76) during the 8-week period following cardioversion. The majority of events in the TEE group occurred in patients whose AF recurred or who were outside of the therapeutic range at the moment of the event, whereas, in the patients who were receiving warfarin, the events occurred in sinus rhythm and within the therapeutic range. It is also interesting to note that fewer bleeding episodes were observed in the TEE-guided group (2.9% versus 5.5%; $p = 0.03$). In this group, time to cardioversion was also shorter (3.0 ± 5.6 days versus 30.6 ± 10.6 days; $p < 0.001$), and the success rate of AF reversal was higher in comparison with the conventional strategy (71% versus 65.2%; $p = 0.03$), although there was no difference in the percentage of patients who remained in sinus rhythm for 8 weeks.¹⁰⁴

In the event that AF lasts less than 48 hours, which is easily determined by inquiring about symptoms, and the patient is not at a high thromboembolism risk (valve disease, ventricular dysfunction, prosthesis, prior history of thromboembolism), the risk of thromboembolism is very low and cardioversion may be performed^{105,106} without prior full anticoagulation. Maintaining anticoagulation for 4 weeks after the procedure is controversial and there are no studies comparing different

heparins or heparins and new anticoagulants for patients with AF lasting less than 48 hours.

In the event of AF lasting less than 48 hours in patients with moderate to high risks of thromboembolic events ($\text{CHA}_2\text{DS}_2\text{-VASc} > 1$), unfractionated or low-molecular weight heparin before cardioversion and long-term maintenance are recommended.⁸⁶

In cases of AF with hemodynamic instability, urgent cardioversion should always be performed, with a pre-procedure heparin bolus.⁸⁶

In relation to heparins, unfractionated heparin has given way to low-molecular weight heparins. Indications for using heparins are: (1) following chemical or electrical cardioversion in hospitalized patients, (2) in combination with oral anticoagulation during INR adjustment; (3) during provisory interruption of warfarin anticoagulation in order to perform diagnostic procedures or therapies with hemorrhage risks (a strategy commonly known as a “heparin bridge”). Although there are 3 types of low-molecular weight heparin (dalteparin, enoxaparin, and nadroparin), enoxaparin has been the most widely used in clinical practice.¹⁰⁷

The flowchart in Figure 2 summarizes recommendations in relation to pericardioversion anticoagulation in atrial fibrillation.

6. Anticoagulation and Antiplatelet Therapy in Patients with Patent Foramen Ovale

6.1. Introduction

Patent foramen ovale (PFO) is the most common congenital heart disease of fetal origin.¹⁰⁸⁻¹¹⁰ It is present in 15% to 35% of the adult population (15% to 25% in studies whose diagnostic method was echocardiogram^{111,112} and 15% to 35% in autopsies).¹¹³⁻¹¹⁵ Several reports exist on the relation between PFO and diverse pathologies, with different strengths of association, including: platypnea-orthodeoxia syndrome,¹¹⁶ decompression syndrome,^{117,118} systemic and coronary embolism,^{119,120} obstructive sleep apnea-hypopnea syndrome (OSAHS),¹²¹ migraine with aura,¹²²⁻¹²⁵ and stroke.¹²⁶

6.2. Relation between Patent Foramen Ovale and Cryptogenic Stroke

The causal relation between PFO and cryptogenic stroke, caused by paradoxical embolism of the right-left shunt, is dubious and much debated within the literature.^{112,127} Meta-analysis data¹²⁸ have established a possible causal relation between PFO and cryptogenic stroke in patients < 55 . Another study¹²⁹ evaluated the presence of PFO using TEE in stroke patients and identified a higher incidence of PFO in cryptogenic stroke patients in comparison with patients with stroke of known cause, both in patients < 55 and in patients > 55 . A retrospective Brazilian study¹³⁰ also identified the presence of PFO as a risk factor for cryptogenic stroke, with an odds ratio of 3.3 in patients with PFO compared to patients without PFO. In prospective population studies, on the other hand, the presence of PFO has not been related to increased stroke risk, either in patients who have already

Statement

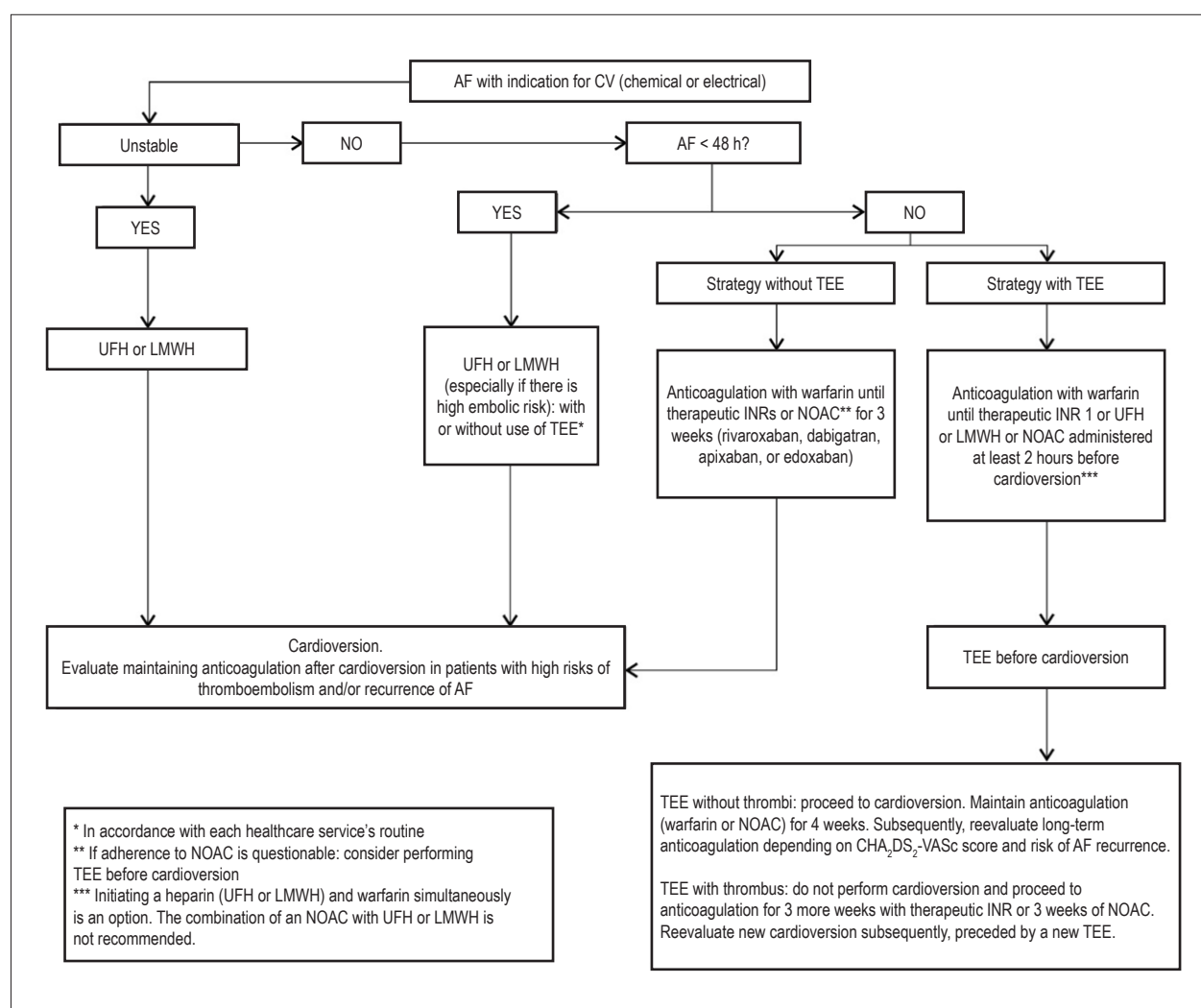


Figure 2 – Recommendations in relation to pericardioversion anticoagulation in atrial fibrillation.

AF: atrial fibrillation; INR: international normalized ratio; LMWH: low-molecular weight heparin; NOAC: new oral anticoagulant; TEE: transesophageal echocardiography; UFH: unfractionated heparin.

suffered a stroke¹³¹ (secondary prevention) or in asymptomatic patients (primary prevention).^{111,132,133}

The conclusion is, thus, that diagnosis of PFO in a patient with cryptogenic stroke does not establish a causal relation between the two entities,¹³⁴ given that the risk attributable to PFO decreases with age and in the presence of risk factors such as systemic arterial hypertension, diabetes mellitus, tobacco use, personal history of transient ischemic attack, or prior stroke.¹³⁵ Based on data from a meta-analysis¹³⁵ of 12 cohort studies which followed cryptogenic stroke patients, the Risk of Paradoxical Embolism (RoPE) score, which quantifies the risk of PFO-attributable stroke (Table 12), was developed. This study provided evidence that patients with higher scores (with increased risks attributable to PFO as a causal factor of stroke) also had lower risks of stroke recurrence during follow up. In conclusion, the causal relation between PFO and stroke continues to be uncertain,

and, even in patients whose stroke mechanism is attributed to PFO/paradoxical embolism, the event recurrence rate is very low (1% to 3% over 2 years in patients with RoPE scores of 9 or 10).^{134,135}

Some echocardiography characteristics of PFO may be related to greater risks of paradoxical embolism, such as: significant right-left shunt, spontaneous right-left shunt, greater PFO flap mobility, prominent Eustachian valve, presence of Chiari network, and atrial septal aneurysm.^{109,136-141} However, some of these characteristics have not been shown to be consistently related to higher rates of embolic events in other studies.^{111,132,142-145}

6.3. Evidence for the Use of Antiplatelet Agents or Anticoagulants in Patients with Patent Foramen Ovale

Given the hypothesis that embolic events related to PFO occur either by paradoxical embolism or embolism of a

Table 12 – Risk of Paradoxical Embolism (RoPE) score. The higher the RoPE score, the higher the causality between patent foramen ovale and stroke

Characteristic	Points
No PH or SAH	1
No PH of diabetes	1
No PH of stroke/TIA	1
Non-smoker	1
Cortical infarct on imaging exam	1
Age (in years):	
18 to 29	5
30 to 39	4
40 to 49	3
50 to 59	2
60 to 69	1
≥ 70	0

PH: personal history; SAH: systemic arterial hypertension; TIA: transient ischemic attack.

thrombus formed in the left atrium, antiplatelet therapy or anticoagulation are justified in the following situations:

Primary prevention: no studies have evaluated primary prevention of embolic events in patients with PFO. Considering that the causal relation between PFO and systemic embolism is still uncertain, that the embolic event rate in patients with PFO alone is extremely low, and that the risks inherent in anticoagulant and antiplatelet therapy are not negligible, the use of antiplatelet agents or anticoagulation are not indicated as primary prevention of embolic events in patients with PFO.¹⁴⁶

Secondary prevention: the best therapeutic strategy after an embolic event in the presence of PFO continues to be the focus of debate and controversy due to the dubious correlation which exists between the 2 phenomena. In 2002, the PICSS substudy of the WARSS study¹⁴⁴ compared the use of warfarin to ASA (325 mg daily) in patients with stroke and PFO, in a subgroup of 265 patients with cryptogenic stroke. There were no statistically significant differences in the rate

of recurrent embolic events between the warfarin and the ASA groups in this situation. Another study¹⁴⁷ randomized 47 patients after cryptogenic stroke to ASA (240 mg daily) or warfarin (with an INR goal of 2 to 3), and the authors did not observe any difference between the risk of ischemic stroke or TIA between the groups. A meta-analysis¹⁴⁸ with data from only 2 randomized studies did not identify differences in favor of warfarin in comparison with ASA in the presence of stroke. Another recent meta-analysis¹⁴⁹ compared the use of antiplatelet agents with oral anticoagulation in patients with cryptogenic stroke, using individual data of 2,385 patients from 12 observational studies, and they did not observe any differences in the rates of recurrent stroke between patients receiving oral anticoagulation or antiplatelet agents. In 2017, the results of the CLOSE study were published, which compared percutaneous PFO closure to medical therapy with antiplatelet therapy or anticoagulation. Statistical analysis was not conducted between the clinical treatment groups, as the study did not recruit the target of 900 patients and the event rate was lower than expected. When evaluating the data in absolute values, however, it is possible to observe an incidence of 3 cases in the anticoagulation group and 7 in the antiplatelet therapy group, with an estimated probability of stroke over 5 years of 1.5% and 3%, respectively.⁴⁵ Percutaneous or surgical PFO closure should also be considered in select cases; this discussion, however, lies beyond the scope of this paper.

There is, thus, insufficient evidence for recommending the preferential use of oral anticoagulation over antiplatelet agents, given the low rate of recurrent embolic events in young patients with cryptogenic stroke. The use of antiplatelet agents, thus, seems to be adequate due to the accumulated risk of hemorrhagic complications in these patients in the event that they receive oral anticoagulation and to the efficacy of antiplatelet agents in reducing the risk of embolic events in the general population, which has already been proven (Table 13). It is worth highlighting that the studies on secondary prevention on which these guidelines are based^{144,147,150} were not designed to demonstrate the superiority of oral anticoagulation over antiplatelet therapy, for which reason they are not statistically powered to provide evidence of any possible benefits of oral anticoagulation over antiplatelet therapy.

Table 13 – Recommendations for the use of antiplatelet agents and anticoagulants in primary and secondary prevention of cryptogenic stroke in patients with patent foramen ovale

Indications	Grade of recommendation	Level of evidence
Patients who are not indicated for anticoagulation for other reasons should be started on antiplatelet therapy as secondary prevention	I	B
Use of warfarin as a first choice following the first event	IIb	B
After a recurrent event while using antiplatelet agents, the use of warfarin with an INR goal between 2 and 3 should be considered	IIa	C
Use of Factor Xa inhibitors or thrombin inhibitors following the first event as an alternative to warfarin	IIb	C
Use of antiplatelet agents or anticoagulants as primary prevention	III	C

INR: international normalized ratio.

Statement

7. Antithrombotic Therapy in Oncology Patients with Thrombocytopenia

7.1. Introduction

Cardiovascular diseases and cancer are the main causes of death in Brazil.¹⁵¹ Advances in treatment of neoplasm have increased survival in this population which has thus gone on to be more exposed to traditional risk factors for developing atherosclerotic disease.

On the other hand, oncology patients, as they are in a pro-inflammatory and pro-thrombotic state, may develop atherosclerosis more quickly, and they have a higher risk of developing ACS.¹⁵²

Neoplasia treatment with radiotherapy and chemotherapy itself has deleterious collateral coronary effects, such as the occurrence of vasospasms and endothelial injuries.¹⁵³

Finally, the presence of thrombocytopenia increases the risk of both bleeding and ischemic phenomena. A retrospective evaluation at the MD Anderson Hospital showed that 39% of patients with ACS had platelet counts of < 100,000 cells/mm³.¹⁵⁴

7.2. Antithrombotic Therapy

There are no randomized studies on antithrombotic therapy in patients with thrombocytopenia, as this population is normally excluded from large clinical trials.

A retrospective study of 70 oncology patients with ACS showed lower 7-day mortality in patients with thrombocytopenia who received ASA.¹⁵⁵

In a case series which evaluated patients with platelet counts > 50,000 cells/mm³ who underwent angioplasty, the use of antiplatelet agents and anticoagulants did not increase the incidence of bleeding events.¹⁵⁶

On the other hand, in patients with platelet counts between 30,000 and 50,000 cells/mm³, the use of ASA and clopidogrel was safe; lower doses of unfractionated heparin (30 IU/kg to 50 IU/kg), however, were enough to reach the therapeutic goal in this population.¹⁵⁶ In patients with platelet counts below 10,000, risks and benefits should be evaluated individually. Platelet transfusion and antiplatelet therapy are a therapeutic possibility (Table 14).¹⁵⁶

There are no studies on new antiplatelet agents or non-vitamin K dependent anticoagulants in this population.

Table 14 – Recommendations for use of antiplatelet agents and anticoagulants in oncology patients with thrombocytopenia

Indications	Grade of recommendation	Level of evidence
Use of acetylsalicylic acid in patients with coronary disease	I	A
Combined use of clopidogrel and acetylsalicylic acid in patients with high-risk acute coronary syndrome or after coronary angioplasty	I	A
Acetylsalicylic acid should always be used at a minimum dose, preferably ≤ 100 mg daily	Ila	C
Use of antiplatelet therapy and/or anticoagulant in acute coronary syndrome patients, even if they have thrombocytopenia	Ila	C
Use of a reduced dose of enoxaparin and unfractionated heparin in patients with platelet count < 50,000. Monitoring of therapeutic goal	Ila	C

References

- Sorensen R, Hansen ML, Abildstrom SZ, Hvelplund A, Andersson C, Jorgensen C, et al. Risk of bleeding in patients with acute myocardial infarction treated with different combinations of aspirin, clopidogrel, and vitamin K antagonists in Denmark: a retrospective analysis of nationwide registry data. *Lancet*. 2009;374(9706):1967-74.
- Hansen ML, Sorensen R, Clausen MT, Fog-Petersen ML, Raunso J, Gadsboll N, et al. Risk of bleeding with single, dual, or triple therapy with warfarin, aspirin, and clopidogrel in patients with atrial fibrillation. *Arch Intern Med*. 2010;170(16):1433-41.
- Dans AL, Connolly SJ, Wallentin L, Yang S, Nakamya J, Brueckmann M, et al. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. *Circulation*. 2013;127(5):634-40.
- Oldgren J, Budaj A, Granger CB, Khder Y, Roberts J, Siegbahn A, et al; RE-DEEM Investigators. Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. *Eur Heart J*. 2011;32(22):2781-9.
- Barnes GD, Gu X, Haymart B, Kline-Rogers E, Almany S, Kozlowski J, et al. The predictive ability of the CHADS2 and CHA2DS2-VASc scores for bleeding risk in atrial fibrillation: the MAQI (2) experience. *Thromb Res*. 2014;134(2):294-9.
- Roldan V, Marin F, Manzano-Fernandez S, Gallego P, Vilchez JA, Valdes M, et al. The HAS-BLED score has better prediction accuracy for major bleeding than CHADS2 or CHA2DS2-VASc scores in anticoagulated patients with atrial fibrillation. *J Am Coll Cardiol*. 2013;62(23):2199-204.
- Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al; ESC Scientific Document Group. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2018;39(1):34-78.
- Levine GN, Bates ER, Bittl JA, Brindis RG, Fihn SD, Fleisher LA. 2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American

- College of Cardiology/American Heart Association Task Force on clinical practice guidelines: an update of the 2011 ACCF/AHA/SCAI Guideline for percutaneous coronary intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the diagnosis and management of patients with stable ischemic heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. *Circulation*. 2016;134(10):e123-55. Erratum in: *Circulation*. 2016;134(10):e192-4.
9. Kereiakes DJ, Yeh RW, Massaro JM, Driscoll-Shempp P, Cutlip DE, Steg PG. Dual Antiplatelet Therapy (DAPT) Study Investigators. Antiplatelet therapy duration following bare metal or drug-eluting coronary stents: the dual antiplatelet therapy randomized clinical trial. *JAMA*. 2015;313(11):1113-21. Erratum in: *JAMA*. 2016;316(1):105; *JAMA*. 2015 Jun 2;313(21):2185.
 10. Urban P, Meredith IT, Abizaid A, Pocock SJ, Carrie D, Naber C, et al; LEADERS FREE Investigators. Polymer-free drug-coated coronary stents in patients at high bleeding risk. *N Engl J Med*. 2015;373(21):2038-47.
 11. Hawn MT, Graham LA, Richman JS, Itani KM, Henderson WG, Maddox TM. Risk of major adverse cardiac events following noncardiac surgery in patients with coronary stents. *JAMA*. 2013;310(14):1462-72. Erratum in: *JAMA*. 2014;311(5):528.
 12. Valgimigli M, Patialiakis A, Thury A, McFadden E, Colangelo S, Campo G, et al; ZEUS Investigators. Zotarolimus-eluting versus bare-metal stents in uncertain drug-eluting stent candidates. *J Am Coll Cardiol*. 2015;65(8):805-15.
 13. Ariotti S, Adamo M, Costa F, Patialiakis A, Briguori C, Thury A, et al; ZEUS Investigators. Is bare-metal stent implantation still justifiable in high bleeding risk patients undergoing percutaneous coronary intervention?: A pre-specified analysis from the ZEUS trial. *JACC Cardiovasc Interv*. 2016;9(5):426-36.
 14. Lamberts M, Olesen JB, Ruwald MH, Hansen CM, Karasoy D, Kristensen SL, et al. Bleeding after initiation of multiple antithrombotic drugs, including triple therapy, in atrial fibrillation patients following myocardial infarction and coronary intervention: a nationwide cohort study. *Circulation*. 2012;126(10):1185-93.
 15. Lamberts M, Gislason GH, Olesen JB, Kristensen SL, Schjerning Olsen AM, et al. Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention. *J Am Coll Cardiol*. 2013;62(11):981-9.
 16. Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herman JP, et al; WOEST Study Investigators. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*. 2013;381(9872):1107-15.
 17. Fiedler KA, Maeng M, Mehili J, Schulz-Schupke S, Byrne RA, Sibbing D, et al. Duration of triple therapy in patients requiring oral anticoagulation after drug-eluting stent implantation: the ISAR-TRIPLE trial. *J Am Coll Cardiol*. 2015;65(16):1619-29.
 18. Gibson CM, Pinto DS, Chi G, Arbetter D, Yee M, Mehran R, et al. Recurrent hospitalization among patients with atrial fibrillation undergoing intracoronary stenting treated with two treatment strategies of rivaroxaban or a dose-adjusted oral vitamin K antagonist treatment strategy. *Circulation*. 2017;135(4):323-33.
 19. Cannon CP, Bhatt DL, Oldgren J, Lip GY, Ellis SG, Kimura T, et al; RE-DUAL PCI Steering Committee and Investigators. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. *N Engl J Med*. 2017;377(16):1513-1524.
 20. Lamberts M, Gislason GH, Lip GY, Lassen JF, Olesen JB, Mikkelsen AP, et al. Antiplatelet therapy for stable coronary artery disease in atrial fibrillation patients taking an oral anticoagulant: a nationwide cohort study. *Circulation*. 2014;129(15):1577-85.
 21. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al; Clopidogrel in Unstable angina to prevent Recurrent Events trial (CURE Investigators. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358(9281):527-33.
 22. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345(7):494-502. Erratum in: *N Engl J Med*. 2001;345(20):1506; *N Engl J Med*. 2001;345(23):1716.
 23. Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med*. 1998;339(23):1665-71.
 24. Bhatt DL, Flather MD, Hacke W, Berger PB, Black HR, Boden WE, et al; CHARISMA Investigators. Patients with prior myocardial infarction, stroke, or symptomatic peripheral arterial disease in the CHARISMA trial. *J Am Coll Cardiol*. 2007;49(19):1982-8.
 25. Steinhubl SR, Berger PB, Mann JT 3rd, Fry ET, DeLago A, Wilmer C, et al; CREDO Investigators. Clopidogrel for the Reduction of Events During Observation. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288(19):2411-20.
 26. Cutlip DE, Baim DS, Ho KK, Popma JJ, Lansky AJ, Cohen DJ, et al. Stent thrombosis in the modern era: a pooled analysis of multicenter coronary stent clinical trials. *Circulation*. 2001;103(15):1967-71.
 27. McFadden EP, Stabile E, Regar E, Cheneau E, Ong AT, Kinnaird T, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet*. 2004;364(9444):1519-21.
 28. Ellis SG, Kereiakes DJ, Metzger DC, Caputo RP, Rizik DG, Teirstein PS, et al; ABSORB III Investigators. Everolimus-eluting bioresorbable scaffolds for coronary artery disease. *N Engl J Med*. 2015;373(20):1905-15.
 29. Cassese S, Byrne RA, Ndrepepa G, Kufner S, Wiebe J, Repp J, et al. Everolimus-eluting bioresorbable vascular scaffolds versus everolimus-eluting metallic stents: a meta-analysis of randomised controlled trials. *Lancet*. 2016;387(10018):537-44.
 30. Serruys PW, Chevalier B, Sotomi Y, Cequier A, Carrie D, Piek JJ, et al. Comparison of an everolimus-eluting bioresorbable scaffold with an everolimus-eluting metallic stent for the treatment of coronary artery stenosis (ABSORB II): a 3 year, randomised, controlled, single-blind, multicentre clinical trial. *Lancet*. 2016;388(10059):2479-91.
 31. Raber L, Brugaletta S, Yamaji K, O'Sullivan CJ, Otsuki S, Koppa T, et al. Very late scaffold thrombosis: intracoronary imaging and histopathological and spectroscopic findings. *J Am Coll Cardiol*. 2015;66(17):1901-14.
 32. Yeh RW, Secemsky EA, Kereiakes DJ, Normand SL, Gershlick AH, Cohen DJ, et al; DAPT Study Investigators. Development and validation of aprediction rule for benefit and harm of dual antiplatelet therapy beyond 1 year after percutaneous coronary intervention. *JAMA*. 2016;315(16):1735-49.
 33. Costa F, van Klaveren D, James S, Heg D, Raber L, Feres F, et al; PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. *Lancet*. 2017;389(10073):1025-34.
 34. Schulz-Schupke S, Byrne RA, Ten Berg JM, Neumann FJ, Han Y, Adriaenssens T, et al; Intracoronary Stenting and Antithrombotic Regimen: Safety And Efficacy of 6 Months Dual Antiplatelet Therapy After Drug-Eluting Stenting (ISAR-SAFE) Trial Investigators. ISAR-SAFE: a randomized, double-blind, placebo-controlled trial of 6 vs. 12 months of clopidogrel therapy after drug-eluting stenting. *Eur Heart J*. 2015;36(20):1252-63.
 35. Gilard M, Barragan P, Noryani AA, Noor HA, Majwal T, Hovasse T, et al. 6- versus 24-month dual antiplatelet therapy after implantation of drug-eluting stents in patients nonresistant to aspirin: the randomized, multicenter ITALIC trial. *J Am Coll Cardiol*. 2015;65(8):777-86.
 36. Colombo A, Chieffo A, Frasieri A, Garbo R, Masotti-Centol M, Salvatella N, et al. Second-generation drug-eluting stent implantation followed by

Statement

- 6- versus 12-month dual antiplatelet therapy: the SECURITY randomized clinical trial. *J Am Coll Cardiol*. 2014;64(20):2086-97.
37. Lee CW, Ahn JM, Park DW, Kang SJ, Lee SW, Kim YH, et al. Optimal duration of dual antiplatelet therapy after drug-eluting stent implantation: a randomized, controlled trial. *Circulation*. 2014;129(3):304-12.
38. Collet JP, Silvain J, Barthelemy O, Range G, Cayla G, Van Belle E, et al; ARCTIC investigators. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. *Lancet*. 2014;384(9954):1577-85.
39. Bittl JA, Baber U, Bradley SM, Wijeyesundera DN. Duration of dual antiplatelet therapy: a systematic review for the 2016 ACC/AHA Guideline focused update on duration of dual antiplatelet therapy in patients with coronary artery disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. *J Am Coll Cardiol*. 2016;68(10):1116-39.
40. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361(11):1045-57.
41. Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, et al; TRITON-TIMI 38 investigators. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet*. 2009;373(9665):723-31.
42. Palmerini T, Della Riva D, Benedetto U, Reggiani LB, Feres F, Abizaid A, et al. Three, six or twelve months of dual antiplatelet therapy after drug-eluting stent implantation in patients with or without acute coronary syndromes: an individual patient data pairwise and network meta-analysis of six randomized trials and 11 473 patients. *Eur Heart J*. 2017;38(14):1034-43.
43. Bonaca MP, Bhatt DL, Cohen M, Steg PG, Storey RF, Jensen EC, et al; PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. *N Engl J Med*. 2015;372(19):1791-800.
44. Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet*. 2014;383(9921):955-62.
45. Majeed A, Hwang HG, Connolly SJ, Eikelboom JW, Ezekowitz MD, Wallentin L, et al. Management and outcomes of major bleeding during treatment with dabigatran or warfarin. *Circulation*. 2013;128(21):2325-32.
46. Raval AN, Cigarroa JE, Chung MK, Diaz-Sandoval LJ, Diercks D, Piccini JP, et al; American Heart Association Clinical Pharmacology Subcommittee of the Acute Cardiac Care and General Cardiology Committee of the Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; and Council on Quality of Care and Outcomes Research. Management of patients on non-vitamin K antagonist oral anticoagulants in the acute care and periprocedural setting: a scientific statement from the American Heart Association. *Circulation*. 2017;135(10):e604-e633. Erratum in: *Circulation*. 2017;135(10):e647; *Circulation*. 2017;135(24):e1144.
47. Levy JH, Ageno W, Chan NC, Crowther M, Verhamme P, Weitz JJ; Subcommittee on Control of Anticoagulation. When and how to use antidotes for the reversal of direct oral anticoagulants: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2016;14(3):623-7.
48. Pollack CV Jr, Reilly PA, Eikelboom J, Glund S, Verhamme P, Bernstein RA, et al. Idarucizumab for dabigatran reversal. *N Engl J Med*. 2015;373(6):511-20.
49. Siegal DM, Curnutte JT, Connolly SJ, Lu G, Conley PB, Wiens BL, et al. Andexanet alfa for the reversal of factor Xa inhibitor activity. *N Engl J Med*. 2015;373(25):2413-24.
50. Connolly SJ, Milling TJ Jr, Eikelboom JW, Gibson CM, Curnutte JT, Gold A, et al; ANNEXA-4 Investigators. Andexanet alfa for acute major bleeding associated with factor Xa inhibitors. *N Engl J Med*. 2016;375(12):1131-41.
51. Stevenson JW, Minns AB, Smollin C, Albertson TE, Cantrell FL, Tomaszewski C, et al. An observational case series of dabigatran and rivaroxaban exposures reported to a poison control system. *Am J Emerg Med*. 2014;32(9):1077-84.
52. Lehmann T, Hofer KE, Baumann M, Hasler K, Ceschi A, Kupferschmidt H, et al. Massive human rivaroxaban overdose. *Thromb Haemost*. 2014;112(4):834-6.
53. Dibu JR, Weimer JM, Ahrens C, Manno E, Frontera JA. The role of FEIBA in reversing novel oral anticoagulants in intracerebral hemorrhage. *Neurocrit Care*. 2015;24(3):413-9.
54. Perzborn E, Heitmeier S, Laux V, Buchmüller A. Reversal of rivaroxaban-induced anticoagulation with prothrombin complex concentrate, activated prothrombin complex concentrate and recombinant activated factor VII in vitro. *Thromb Res*. 2014;133(4):671-81.
55. Schultz NH, Tran HTT, Bjørnsen S, Henriksson CE, Sandset PM, Holme PA. The reversal effect of prothrombin complex concentrate (PCC), activated PCC and recombinant activated factor VII against anticoagulation of Xa inhibitor. *Thromb J*. 2017 Feb 20;15:6.
56. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation*. 2011;124(14):1573-9.
57. Gehrie E, Tormey C. Novel oral anticoagulants: efficacy, laboratory measurement, and approaches to emergent reversal. *Arch Pathol Lab Med*. 2015;139(5):687-92.
58. Zimerman LI, Fenelon G, Martinelli Filho M, Grupi C, Atiél, Lorga Filho A, et al; Sociedade Brasileira de Cardiologia. Diretrizes brasileiras de fibrilação atrial. *Arq Bras Cardiol*. 2009;92(6 suppl 1):1-39.
59. 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(4 Supl.2):1-22.
60. Benjamin EJ, Wolf PA, D'Agostino RB, Silbershatz H, Kannel WB, Levy D. Impact of atrial fibrillation on the risk of death: the Framingham Heart Study. *Circulation*. 1998;98(10):946-52.
61. Psaty BM, Manolio TA, Kuller LH, Kronmal RA, Cushman M, Fried LP, et al. Incidence of and risk factors for atrial fibrillation in older adults. *Circulation*. 1997;96(7):2455-61.
62. Soliman EZ, Prineas RJ, Case LD, Zhang Z, Goff DC Jr. Ethnic distribution of ECG predictors of atrial fibrillation and its impact on understanding the ethnic distribution of ischemic stroke in the Atherosclerosis Risk in Communities (ARIC) study. *Stroke*. 2009;40(4):1204-11. Erratum in: *Stroke*. 2010;41(5):e433.
63. Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation: analysis and implications. *Arch Intern Med*. 1995;155(5):469-73.
64. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke*. 1991;22(8):983-8.
65. Gorter JW. Major bleeding during anticoagulation after cerebral ischemia: patterns and risk factors. *Stroke Prevention In Reversible Ischemia Trial (SPIRIT)*. European Atrial Fibrillation Trial (EAFT) study groups. *Neurology*. 1999;53(6):1319-27.
66. Watson T, Kakar P, Lip GY. Stroke risk stratification in atrial fibrillation: something to EXAMINE more closely. *Int J Clin Pract*. 2007;61(1):6-9. Erratum in: *Int J Clin Pract*. 2007;61(3):534.
67. Das RR, Seshadri S, Beiser AS, Kelly-Hayes M, Au R, Himali JJ. Prevalence and correlates of silent cerebral infarcts in the Framingham Offspring Study. *Stroke*. 2008;39(11):2929-35.
68. Sherman DG. Stroke prevention in atrial fibrillation: pharmacological rate versus rhythm control. *Stroke*. 2007;38(2 Suppl):615-7.
69. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al; Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347(23):1825-33.
70. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, et al; ACC/AHA Task Force Members. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary:

- a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130(23):2071-104. Erratum in: *Circulation*. 2014;130(23):e270-1.
71. Bungard TJ, Ackman ML, Ho G, Tsuyuki RT. Adequacy of anticoagulation in patients with atrial fibrillation coming to a hospital. *Pharmacotherapy*. 2000;20(9):1060-5.
 72. Go AS, Hylek EM, Borowsky LH, Phillips KA, Selby JV, Singer DE. Warfarin use among ambulatory patients with nonvalvular atrial fibrillation: the Anticoagulation and Risk Factors in Atrial Fibrillation (ATRIA) study. *Ann Intern Med*. 1999;131(12):927-34.
 73. Szekely P. Systemic embolism and anticoagulant prophylaxis in rheumatic heart disease. *Br Med J*. 1964;1(5392):1209-12.
 74. Stewart RA. Clinical trials of direct thrombin and factor Xa inhibitors in atrial fibrillation. *Curr Opin Cardiol*. 2011;26(4):294-9.
 75. Berger M, Schweitzer P. Timing of thromboembolic events after electrical cardioversion of atrial fibrillation or flutter: a retrospective analysis. *Am J Cardiol*. 1998;82(12):1545-7.
 76. Nagarakanti R, Ezekowitz MD, Oldgren J, Yang S, Chernick M, Aikens TH, et al. Dabigatran versus warfarin in patients with atrial fibrillation: an analysis of patients undergoing cardioversion. *Circulation*. 2011;123(2):131-6.
 77. Flaker G, Lopes RD, Al-Khatib SM, Hermosillo AG, Hohnloser SH, Tinga B, et al; ARISTOTLE Committees and Investigators. Efficacy and safety of apixaban in patients after cardioversion for atrial fibrillation: insights from the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation). *J Am Coll Cardiol*. 2014;63(11):1082-7.
 78. Cappato R, Ezekowitz MD, Klein AL, Camm AJ, Ma CS, Le Heuzey JY, et al; X-VerT Investigators. Rivaroxaban vs. vitamin K antagonists for cardioversion in atrial fibrillation. *Eur Heart J*. 2014;35(47):3346-55.
 79. Goette A, Merino JL, Ezekowitz M, Zamoryakhin D, Melino M, Jin J, et al; ENSURE-AF investigators. Edoxaban versus enoxaparin-warfarin in patients undergoing cardioversion of atrial fibrillation (ENSURE-AF): a randomised, open-label, phase 3B trial. *Lancet*. 2016;388(10055):1995-2003.
 80. Kinch JW, Davidoff R. Prevention of embolic events after cardioversion of atrial fibrillation. Current and evolving strategies. *Arch Intern Med*. 1995;155(13):1353-60.
 81. Gentile F, Elhendy A, Khandheria BK, Seward JB, Lohse CM, Shen WK, et al. Safety of electrical cardioversion in patients with atrial fibrillation. *Mayo Clin Proc*. 2002;77(9):897-904.
 82. Arnold AZ, Mick MJ, Mazurek RP, Loop FD, Trohman RG. Role of prophylactic anticoagulation for direct current cardioversion in patients with atrial fibrillation or atrial flutter. *J Am Coll Cardiol*. 1992;19(4):851-5.
 83. Khan IA. Atrial stunning: basic and clinical considerations. *Int J Cardiol*. 2003;92(2-3):113-28.
 84. Manning WJ, Silverman DI, Katz SE, Riley MF, Come PC, Doherty RM, et al. Impaired left atrial mechanical function after cardioversion: relation to the duration of atrial fibrillation. *J Am Coll Cardiol*. 1994;23(7):1535-40.
 85. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. ESC Scientific Document Group. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37(38):2893-962.
 86. Pritchett EL. Management of atrial fibrillation. *N Engl J Med*. 1992;326(19):1264-71.
 87. 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.
 88. Botkin SB, Dhanekula LS, Olshansky B. Outpatient cardioversion of atrial arrhythmias: efficacy, safety, and costs. *Am Heart J*. 2003;145(2):233-8.
 89. Singer DE, Hughes RA, Gress DR, Sheehan MA, Oertel LB, Maraventano SW, et al; Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The effect of low-dose warfarin on the risk of stroke in patients with nonrheumatic atrial fibrillation. *N Engl J Med*. 1990;323(22):1505-11.
 90. Stroke Prevention in Atrial Fibrillation Study. Final results. *Circulation*. 1991;84(2):527-39.
 91. Warfarin versus aspirin for prevention of thromboembolism in atrial fibrillation: Stroke Prevention in Atrial Fibrillation II Study. *Lancet*. 1994;343(8899):687-91.
 92. Petersen P, Boysen G, Godtfredsen J, Andersen ED, Andersen B. Placebo-controlled, randomised trial of warfarin and aspirin for prevention of thromboembolic complications in chronic atrial fibrillation. The Copenhagen AFASAK study. *Lancet*. 1989;1(8631):175-9.
 93. Ezekowitz MD, Bridgers SL, James KE, Carliner NH, Colling CL, Gornick CC, et al. Warfarin in the prevention of stroke associated with nonrheumatic atrial fibrillation. Veterans Affairs Stroke Prevention in Nonrheumatic Atrial Fibrillation Investigators. *N Engl J Med*. 1992;327(20):1406-12. Erratum in: *N Engl J Med* 1993;328(2):148.
 94. Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol*. 1991;18(2):349-55.
 95. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med*. 1994;154(13):1449-57. Erratum in: *Arch Intern Med*. 1994;154(19):2254.
 96. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med*. 2007;146(12):857-67.
 97. van Walraven C, Hart RG, Singer DE, Laupacis A, Connolly S, Petersen P, et al. Oral anticoagulants vs aspirin in nonvalvular atrial fibrillation: an individual patient meta-analysis. *JAMA*. 2002;288(19):2441-8.
 98. Cooper NJ, Sutton AJ, Lu G, Khunti K. Mixed comparison of stroke prevention treatments in individuals with nonrheumatic atrial fibrillation. *Arch Intern Med*. 2006;166(12):1269-75.
 99. Piccini JP, Stevens SR, Lokhnygina Y, Patel MR, Halperin JL, Singer DE, et al; ROCKET AF Steering Committee & Investigators. Outcomes after cardioversion and atrial fibrillation ablation in patients treated with rivaroxaban and warfarin in the ROCKET AF trial. *J Am Coll Cardiol*. 2013;61(19):1998-2006.
 100. Pallisgaard JL, Lindhardt TB, Hansen ML, Schjerning AM, Olesen JB, Staerk L, et al. Cardioversion and risk of adverse events with dabigatran versus warfarin: a nationwide cohort study. *PLoS One*. 2015;10(10):e0141377.
 101. Nuotio I, Hartikainen JE, Gronberg T, Biancari F, Airaksinen KE. Time to cardioversion for acute atrial fibrillation and thromboembolic complications. *JAMA*. 2014;312(6):647-9.
 102. Klein AL, Grimm RA, Murray RD, Apperson-Hansen C, Asinger RW, Black IW, et al; Assessment of Cardioversion Using Transesophageal Echocardiography Investigators. Use of transesophageal echocardiography to guide cardioversion in patients with atrial fibrillation. *N Engl J Med*. 2001;344(19):1411-20.
 103. Bartel T, Erbel R; Acute Trial Investigators. Transoesophageal echocardiography for immediate and safe cardioversion in patients with atrial fibrillation. *Eur Heart J*. 2001;22(22):2041-4.
 104. Gallagher MM, Hennessy BJ, Edvardsson N, Hart CM, Shannon MS, Obel OA, et al. Embolic complications of direct current cardioversion of atrial arrhythmias: association with low intensity of anticoagulation at the time of cardioversion. *J Am Coll Cardiol*. 2002;40(5):926-33.
 105. Weigner MJ, Caulfield TA, Danias PC, Silverman DI, Manning WJ. Risk for clinical thromboembolism associated with conversion to sinus rhythm in patients with atrial fibrillation lasting less than 48 hours. *Ann Intern Med*. 1997;126(8):615-20.
 106. Kim M, Trohman R, Eagle K. Low molecular weight heparin in atrial fibrillation management: facts, fiction, future. *Card Electrophysiol Rev*. 2003;7(4):397-400.
 107. Serrano Junior CV, Fenelon G, Soeiro AM, Nicolau JC, Piegas LS, Montenegro ST, et al. Sociedade Brasileira de Cardiologia. Diretrizes

Statement

- Brasileiras de antiagregantes plaquetários e anticoagulantes em cardiologia. *Arq Bras Cardiol.* 2013;101(3 Supl.3):1-93.
108. Hara H, Virmani R, Ladich E, Mackey-Bojack S, Titus J, Reisman M, et al. Patent foramen ovale: current pathology, pathophysiology, and clinical status. *J Am Coll Cardiol.* 2005;46(9):1768-76.
 109. Wu LA, Malouf JF, Dearani JA, Hagler DJ, Reeder GS, Petty GW, et al. Patent foramen ovale in cryptogenic stroke: current understanding and management options. *Arch Intern Med.* 2004;164(9):950-6.
 110. Kerut EK, Norfleet WT, Plotnick GD, Giles TD. Patent foramen ovale: a review of associated conditions and the impact of physiological size. *J Am Coll Cardiol.* 2001;38(3):613-23.
 111. Meissner I, Khandheria BK, Heit JA, Petty GW, Sheps SG, Schwartz GL, et al. Patent foramen ovale: innocent or guilty? Evidence from a prospective population-based study. *J Am Coll Cardiol.* 2006;47(2):440-5.
 112. Di Tullio MR. Patent foramen ovale: echocardiographic detection and clinical relevance in stroke. *J Am Soc Echocardiogr.* 2010;23(2):144-55.
 113. Penther P. [Patent foramen ovale: an anatomical study. Apropos of 500 consecutive autopsies]. *Arch Mal Coeur Vaiss.* 1994;87(1):15-21.
 114. Schroeckenstein RF, Wasenda GJ, Edwards JE. Valvular competent patent foramen ovale in adults. *Minn Med.* 1972;55(1):11-3.
 115. Hagen PT, Scholz DG, Edwards WD. Incidence and size of patent foramen ovale during the first 10 decades of life: an autopsy study of 965 normal hearts. *Mayo Clin Proc.* 1984;59(1):17-20.
 116. Rigatelli G, Ronco F. Patent foramen ovale: a comprehensive review for pulmonologists. *Curr Opin Pulm Med.* 2010;16(5):442-7.
 117. Billinger M, Zbinden R, Mordasini R, Windecker S, Schwerzmann M, Meier B, et al. Patent foramen ovale closure in recreational divers: effect on decompression illness and ischaemic brain lesions during long-term follow-up. *Heart.* 2011;97(23):1932-7.
 118. Torti SR, Billinger M, Schwerzmann M, Vogel R, Zbinden R, Windecker S, et al. Risk of decompression illness among 230 divers in relation to the presence and size of patent foramen ovale. *Eur Heart J.* 2004;25(12):1014-20.
 119. Wohrle J, Kochs M, Hombach V, Merkle N. Prevalence of myocardial scar in patients with cryptogenic cerebral ischemic events and patent foramen ovale. *JACC Cardiovasc Imaging.* 2010;3(8):833-9.
 120. Neisius U, Northridge DB, Cruden NL, Denver MA. Myocardial infarction associated with patent foramen ovale and paradoxical embolism: case series. *Int J Cardiol.* 2015 Feb 1;180:34-7.
 121. Lau EM, Yee BJ, Grunstein RR, Celemajer DS. Patent foramen ovale and obstructive sleep apnea: a new association? *Sleep Med Rev.* 2010;14(6):391-5.
 122. Sevgi EB, Erdener SE, Demirci M, Topcuoglu MA, Dalkara T. Paradoxical air microembolism induces cerebral bioelectrical abnormalities and occasionally headache in patent foramen ovale patients with migraine. *J Am Heart Assoc.* 2012;1(6):e001735.
 123. Rundek T, Elkind MS, Di Tullio MR, Carrera E, Jin Z, Sacco RL, et al. Patent foramen ovale and migraine: a cross-sectional study from the Northern Manhattan Study (NOMAS). *Circulation.* 2008;118(14):1419-24. Erratum in: *Circulation.* 2008;118(18):e682.
 124. Lip PZ, Lip GY. Patent foramen ovale and migraine attacks: a systematic review. *Am J Med.* 2014;127(5):411-20.
 125. Dowson A, Mullen MJ, Peatfield R, Muir K, Khan AA, Wells C, et al. Migraine Intervention With STARFlex Technology (MIST) trial: a prospective, multicenter, double-blind, sham-controlled trial to evaluate the effectiveness of patent foramen ovale closure with STARFlex septal repair implant to resolve refractory migraine headache. *Circulation.* 2008;117(11):1397-404. Erratum in: *Circulation.* 2009;120(9):e71-2.
 126. Cohnheim JF. *Vorlesungen Über Allgemeine Pathologie.* 2nd ed. Berlin: August Hirschwald; 1987.
 127. Rundek T. PFO in stroke: a direct association or coincidence? *Eur J Neurol.* 2008;15(9):887-8.
 128. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology.* 2000;55(8):1172-9.
 129. Handke M, Harloff A, Olschewski M. Patent foramen ovale and cryptogenic stroke in older patients. *N Engl J Med.* 2007;357(22):2262-8.
 130. Negrão EM, Brandi IV, Nunes SV, Távaro DG, Nakayama M, Beraldo PS. Patent foramen ovale and ischemic stroke in young people: statistical association or causal relation? *Arq Bras Cardiol.* 2007;88(5):514-20.
 131. Katsanos AH, Spence JD, Bogiatzi C, Parisis J, Giannopoulos S, Frogoudaki A, et al. Recurrent stroke and patent foramen ovale: a systematic review and meta-analysis. *Stroke.* 2014;45(11):3352-9.
 132. Di Tullio MR, Sacco RL, Sciacca RR, Jin Z, Homma S. Patent foramen ovale and the risk of ischemic stroke in a multiethnic population. *J Am Coll Cardiol.* 2007;49(7):797-802.
 133. Di Tullio MR, Jin Z, Russo C, Elkind MS, Rundek T, Yoshita M, et al. Patent foramen ovale, subclinical cerebrovascular disease, and ischemic stroke in a population-based cohort. *J Am Coll Cardiol.* 2013;62(1):35-41.
 134. Homma S, M Steven, Rundek T, Yee-Ping S, Franke J, Davidson K, et al. Patent foramen ovale. *Nature Reviews Disease Primer.* 2016 Jan;2:15087.
 135. Kent DM, Ruthazer R, Weimar C, Mas JL, Serena J, Homma S, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. *Neurology.* 2013;81(7):619-25.
 136. Schuchlenz HW, Weihs W, Horner S, Quehenberger F. The association between the diameter of a patent foramen ovale and the risk of embolic cerebrovascular events. *Am J Med.* 2000;109(6):456-62.
 137. Homma S, Di Tullio MR, Sacco RL, Mihalatos D, Li Mandri G, Mohr JP. Characteristics of patent foramen ovale associated with cryptogenic stroke. A biplane transesophageal echocardiographic study. *Stroke.* 1994;25(3):582-6.
 138. De Castro S, Cartoni D, Fiorelli M, Rasura M, Anzini A, Zanette EM. Morphological and functional characteristics of patent foramen ovale and their embolic implications. *Stroke.* 2000;31(10):2407-13.
 139. Stone DA, Godard J, Corretti MC, Kittner SJ, Sample C, Price TR. Patent foramen ovale: association between the degree of shunt by contrast transesophageal echocardiography and the risk of future ischemic neurologic events. *Am Heart J.* 1996;131(1):158-61.
 140. Hanna JP, Sun JP, Furlan AJ, Stewart WJ, Sila CA, Tan M. Patent foramen ovale and brain infarct. Echocardiographic predictors, recurrence, and prevention. *Stroke.* 1994;25(4):782-6.
 141. Rigatelli G, Dell'avvocata F, Braggion G, Giordan M, Chinaglia M, Cardaioli P. Persistent venous valves correlate with increased shunt and multiple preceding cryptogenic embolic events in patients with patent foramen ovale: an intracardiac echocardiographic study. *Catheter Cardiovasc Interv.* 2008;72(7):973-6.
 142. Serena J, Martí-Fàbregas J, Santamarina E, Rodríguez JJ, Pérez-Ayuso MJ, Masjuan J, et al. Recurrent stroke and massive right-to-left shunt: results from the prospective Spanish multicenter (CODICIA) study. *Stroke.* 2008;39(12):3131-6.
 143. Mas JL, Arquizan C, Lamy C, Zuber M, Cabanes L, Derumeaux G, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med.* 2001;345(24):1740-6.
 144. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP; PFO in Cryptogenic Stroke Study (PICSS) Investigators. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation.* 2002;105(22):2625-31.
 145. Petty GW, Khandheria BK, Meissner I, Whisnant JP, Rocca WA, Christianson TJ, et al. Population-based study of the relationship between patent foramen ovale and cerebrovascular ischemic events. *Mayo Clin Proc.* 2006;81(5):602-8.
 146. Meschia J, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2014; 45(12):3754-832.
 147. Shariat A, Yaghoubi E, Farazdaghi M, Aghasadeghi K, Borhani Haghighi A. Comparison of medical treatments in cryptogenic stroke patients

- with patent foramen ovale: a randomized clinical trial. *J Res Med Sci*. 2013;18(2):94-8.
148. Messé SR, Gronseth G, Kent DM, Kizer JR, Homma S, Rosterman L, et al. Practice advisory: Recurrent stroke with patent foramen ovale (update of practice parameter) Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2016;87(8):815-21.
 149. Kent DM, Dahabreh IJ, Ruthazer R, Furlan AJ, Weimar C, Serena J, et al. Anticoagulant vs. antiplatelet therapy in patients with cryptogenic stroke and patent foramen ovale: an individual participant data meta-analysis. *Eur Heart J*. 2015;36(35):2381-9.
 150. Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, et al; CLOSE Investigators. Patent foramen ovale closure or anticoagulation vs antiplatelets after stroke. *N Engl J Med*. 2017;377(11):1011-21.
 151. Brasil. Ministério da Saúde. DATASUS. [Internet]. Acesso em 2017 dez 1]. Disponível em: <http://tabnet.datasus.gov.br/cgi/tabcgi.exe?sim/cnv/obt10uf.def>
 152. Chang HM, Moudgil R, Scarabelli T, Okwuosa TM, Yeh ET. Cardiovascular complications of cancer therapy best practices in diagnosis, prevention, and management: part 1. *J Am Coll Cardiol*. 2017;70(20):2536-51.
 153. Mosseri M, Fingert HJ, Varticovski L, Chokshi S, Isner JM. In vitro evidence that myocardial ischemia resulting from 5-fluorouracil chemotherapy is due to protein kinase C-mediated vasoconstriction of vascular smooth muscle. *Cancer Res*. 1993;53(13):3028-33.
 154. Yusuf SW, Iliescu C, Bathina JD, Daher IN, Durand JB. Antiplatelet therapy and percutaneous coronary intervention in patients with acute coronary syndrome and thrombocytopenia. *Tex Heart Inst J*. 2010;37(3):336-40.
 155. Sarkiss MG, Yusuf SW, Warneke CL, Botz C, Lakkis N, Hirsch-Ginsburg C, et al. Impact of aspirin therapy in cancer patients with thrombocytopenia and acute coronary syndromes. *Cancer*. 2007;109(3):621-7.
 156. Iliescu C, Durand J-B, Kroll M. Cardiovascular Interventions in thrombocytopenic cancer Patients. *Tex Heart Inst J*. 2011;38(3):259-60.

Statement



Position Statement on Indications of Echocardiography in Adults – 2019

Development: Cardiovascular Imaging Department (Departamento de Imagem Cardiovascular – DIC) of the Brazilian Society of Cardiology (Sociedade Brasileira de Cardiologia – SBC)

Norms and Guidelines Council: Fernando Bacal, Leandro Ioschpe Zimerman, Paulo Ricardo Avancini Caramori and Pedro A. Lemos

Norms and Guidelines Coordinator: Ludhmila Abrahão Hajjar

Coordinator Editor: Silvio Henrique Barberato

Co-editors: Minna Moreira Dias Romano e Samira Saady Morhy

Statement Authors: Silvio Henrique Barberato,^{1,2,10} Minna Moreira Dias Romano,³ Adenvalva Lima de Souza Beck,^{4,5} Ana Clara Tude Rodrigues,⁶ André Luiz Cerqueira de Almeida,⁷ Bruna Morhy Borges Leal Assunção,^{8,9} Eliza de Almeida Gripp,^{10,11,12} Fabio Villaça Guimarães Filho,¹³ Henry Abensur,¹⁴ José Maria Del Castillo,¹⁵ Marcelo Haertel Miglioranza,^{5,16} Marcelo Luiz Campos Vieira,^{17,18} Márcio Vinicius Lins de Barros,^{19,20,21} Maria do Carmo Pereira Nunes,²² Maria Estefania Bosco Otto,⁴ Renato de Aguiar Hortegal,¹⁴ Rodrigo Bellio de Mattos Barretto,²³ Thais Harada Campos,^{24,25} Vicente Nicolliello de Siqueira,²⁶ Samira Saady Morhy¹⁸

CardioEco-Centro de Diagnóstico Cardiovascular,¹ Curitiba, PR – Brazil

Quanta Diagnóstico e Terapia,² Curitiba, PR – Brazil

Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (FMRP-USP),³ Ribeirão Preto, SP – Brazil

Instituto de Cardiologia do Distrito Federal,⁴ Brasília, DF – Brazil

Fundação Universitária de Cardiologia (ICDF/FUC),⁵ Brasília, DF – Brazil

Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (HC-FMUSP),⁶ São Paulo, SP – Brazil

Santa Casa de Misericórdia de Feira de Santana,⁷ Feira de Santana, BA – Brazil

Instituto do Câncer do Estado de São Paulo (ICESP),⁸ São Paulo, SP – Brazil

Hospital Sírio-Libanês,⁹ São Paulo, SP – Brazil

Hospital Pró-Cardíaco,¹⁰ Rio de Janeiro, RJ – Brazil

Hospital Universitário Antônio Pedro,¹¹ Niterói, RJ – Brazil

DASA,¹² São Paulo, SP – Brazil

Faculdade de Medicina de Marília,¹³ Marília, SP – Brazil

Hospital Beneficência Portuguesa de São Paulo,¹⁴ São Paulo, SP – Brazil

Pronto Socorro Cardiológico de Pernambuco (PROCAPE - UPE),¹⁵ Recife, PE – Brazil

Instituto de Cardiologia de Porto Alegre,¹⁶ Porto Alegre, RS – Brazil

Instituto do Coração do Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo (InCor-HCFMUSP),¹⁷ São Paulo, SP – Brazil

Hospital Israelita Albert Einstein,¹⁸ São Paulo, SP – Brazil

Faculdade de Saúde e Ecologia Humana (FASEH),¹⁹ Vespasiano, MG – Brazil

Rede Materdei de Saúde, Belo Horizonte,²⁰ MG – Brazil

Hospital Vera Cruz,²¹ Belo Horizonte, MG – Brazil

Universidade Federal de Minas Gerais,²² Belo Horizonte, MG – Brazil

Instituto Dante Pazzanese de Cardiologia,²³ São Paulo, SP – Brazil

Diagnoson-Fleury,²⁴ Salvador, BA – Brazil

Hospital Ana Nery,²⁵ Salvador, BA – Brazil

Universidade Federal de São Paulo (UNIFESP),²⁶ São Paulo, SP – Brazil

These statement should be cited as:

Barberato SH, Romano MMD, Beck ALS, Rodrigues ACT, Almeida ALC, Assunção BMBL, et al. Position Statement on Indications of Echocardiography in Adults – 2019. Arq Bras Cardiol. 2019; 113(1):135-181.

Note: The purpose of these Guidelines is to inform. They do not substitute the clinical judgment of doctors who, in final analysis, must determine which tests and treatments are appropriate for their patients.

Corresponding Address: : Sociedade Brasileira de Cardiologia – Av. Marechal Câmara, 360/330 – Centro – Rio de Janeiro – Postal Code: 20020-907. E-mail: sbc@cardiol.br

Statement

Declaration of potential conflict of interest of authors/collaborators of Updated Geriatric Cardiology Guidelines of the Brazilian Society of Cardiology – 2019 If the last three years the author/developer of the Updated:

Names Members of the Statement	Participated in clinical studies and/or experimental trials supported by pharmaceutical or equipment related to the guideline in question	Has spoken at events or activities sponsored by industry related to the guideline in question	It was (is) advisory board member or director of a pharmaceutical or equipment	Committees participated in completion of research sponsored by industry	Personal or institutional aid received from industry	Produced scientific papers in journals sponsored by industry	It shares the industry
Adenvalva Lima de Souza Beck	No	No	No	No	No	No	No
Ana Clara Tude Rodrigues	No	No	No	No	No	No	No
André Luiz Cerqueira de Almeida	No	No	No	No	No	No	No
Bruna Morhy Borges Leal Assunção	No	No	No	No	No	No	No
Eliza de Almeida Gripp	No	No	No	No	No	No	No
Fabio Villaga Guimarães Filho	No	No	No	No	No	No	No
Henry Abensur	No	No	No	No	No	No	No
José Maria Del Castillo	No	No	No	No	No	No	No
Marcelo Haertel Miglioranza	No	No	No	No	No	No	No
Marcelo Luiz Campos Vieira	No	No	No	No	No	No	No
Márcio Vinicius Lins de Barros	No	No	No	No	No	No	No
Maria do Carmo Pereira Nunes	No	No	No	No	No	No	No
Maria Estefânia Bosco Otto	No	No	No	No	No	No	No
Minna Moreira Dias Romano	No	No	No	No	No	No	No
Renato de Aguiar Hortegal	No	No	No	No	No	No	No
Rodrigo Bellio de Mattos Barretto	No	No	No	No	No	No	No
Samira Saady Morhy	No	No	No	No	No	No	No
Silvio Henrique Barberato	No	No	No	No	No	No	No
Thais Harada Campos	No	No	No	No	No	No	No
Vicente Nicolielo de Siqueira	No	No	No	No	No	No	No

Content

1. Introduction	138
2. Evaluation of Heart Function and Structure	139
2.1. Left Ventricular Systolic Function	139
2.2. Left Ventricular Diastolic Function	140
2.3. Cardiomyopathies	140
2.3.1. Dilated Cardiomyopathy	141
2.3.2. Chagasic Dilated Cardiomyopathy	141
2.3.3. Cardiac Resynchronization Therapy and Pacemaker Optimization	141
2.3.4. Assessment after Heart Transplantation	142
2.3.5. Monitoring of Cardiac Function During Chemotherapy with Cardiotoxic Drugs	143
2.3.6. Hypertrophic Cardiomyopathy	145
2.3.7. Restrictive Cardiomyopathies	145
2.3.8. Arrhythmogenic Cardiomyopathy (Right Ventricle Arrhythmogenic Dysplasia)	146
2.3.9. Non-compaction Cardiomyopathy	147
2.4. Arterial Hypertension and Myocardial Hypertrophy	148
2.5. Athletes	149
3. Heart Murmurs, Valvular Heart Disease, Valvular Prostheses and Endocarditis	150
3.1. Heart Murmurs	150
3.2. Native Valves	150
3.2.1. Mitral Regurgitation	150
3.2.2. Mitral Stenosis	151
3.2.3. Aortic Stenosis	153
3.2.4. Aortic Regurgitation	154
3.2.5. Tricuspid Valvopathy	154
3.2.6. Pulmonary Valvopathy	154
3.2.7. Associated Valvar Lesions	155
3.3. Valve Prostheses	158
3.4. Infective Endocarditis	160
4. Hypertension and Pulmonary Thromboembolism	160
5. Coronary Artery Disease	161
5.1. Introduction	161
5.2. Acute Coronary Syndrome	161
5.2.1. Transthoracic Echocardiography	161
5.2.2. Stress Echocardiography	162
5.2.3. Contrast Echocardiography	162
5.3. Chronic Coronary Artery Disease	163
5.3.1. Transthoracic Echocardiography	163
5.3.2. Stress Echocardiography	163
5.3.3. Contrast Echocardiography	163
6. Evaluation of Emboligenic Sources and Cardioembolic Diseases	164
7. Atrial Fibrillation	166
8. Heart Tumors and Masses	166
9. Pericardial Diseases	167
10. Systemic Diseases	168
10.1. Introduction	168
10.2. Chronic Renal Failure	168
10.3. Amyloidosis	168
10.4. Sarcoidosis	168
10.5. Neoplasms	168
10.6. Autoimmune Diseases	168
11. Diseases of The Aorta, Pulmonary Artery and Veins	168
11.1. Aorta	168
11.2. Pulmonary Artery	169
11.3. Veins	169

12. Intraoperative Echocardiography in Cardiac and Non-Cardiac Surgeries	169
12.1. Introduction	169
12.2. Modalities of Intraoperative Echocardiography	169
12.3. Recommendations in Cardiac and Thoracic Aorta Surgery	169
12.4. Recommendations in Non-Cardiac Surgeries	170
13. Echocardiography in Percutaneous Interventions	170
13.1. Introduction	170
13.2. Follow-up of Interventions in Congenital Heart Diseases	170
13.3. Electrophysiology Procedures	171
13.4. Alcoholic Ablation in Hypertrophic Cardiomyopathy	171
13.5. Left Atrial Appendage Occlusion	171
13.6. Treatment of Heart Valves	171
13.7. Treatment of Prosthetic Dysfunction	171
References	172

1. Introduction

In accordance with the “Standards for the Elaboration of Guidelines, Positions and Normations” sanctioned by the Brazilian Society of Cardiology, this document was written to update the “Echocardiography Indication Guidelines” of 2009. The new document is not intended to be a comprehensive review of echocardiography, but rather an indispensable basic guide to support the rational clinical decision-making of the physician requesting the exam for adult patients. Although it considers the recent technological advances of echocardiography, its purpose is not to describe in detail echocardiography methods, but to summarize in a clear and concise way the main situations in which echocardiography brings benefit to the diagnosis and/or therapeutic orientation of the individual. This manuscript chose to highlight the class of recommendation, as described below:

- Class I: conditions for which there is conclusive evidence or, in the absence thereof, general agreement that the examination procedure is useful and safe.

- Class II: conditions for which there is conflicting evidence and/or divergence of opinion on the utility and/or safety of the examination.

- Class IIa: evidence or opinions favorable to the examination. Most experts approve.

- Class IIb: utility and/or safety less well established, with divergent opinions.

- Class III: conditions for which there is evidence or consensus that the examination is not useful and, in some cases, may even be harmful.

In addition, the level of evidence was also described, as follows:

- A: several concordant randomized clinical trials or robust meta-analyses;

- B: less robust meta-analysis data or single randomized clinical study or observational studies;

- C: expert opinion.

Statement

Thus, it was agreed that all the tables with recommendations for the use of echocardiography in the different clinical scenarios include columns with class of recommendation and level of evidence.

2. Evaluation of Heart Function and Structure

2.1. Left Ventricular Systolic Function

The analysis of left ventricular (LV) systolic function is a primary indication of the use of echocardiography. Echocardiographic analysis of LV systolic function can be performed using older techniques such as M-mode, 2D echocardiography, and even more modern techniques, such as three-dimensional (3D) echocardiography or research of myocardial deformation (strain). The M-mode has been used since the 1950s for cardiac structural analysis and provides widely standardized measurements^{1,2} of the dimensions of the cavity and the thickness of the LV. Thus, parameters of ventricular systole analysis are derived as: (1) percentage of systolic shortening of the left ventricular dimension, represented by the difference between the final diastolic and the final systolic dimensions, divided by the final diastolic one; (2) mean corrected circumferential shortening velocity, corresponding to the ratio between the percentage of systolic shortening of the left ventricular dimension divided by the ejection time corrected by the preceding R-R interval (ejection time divided by the square root of the R-R interval); (3) ventricular volumes at the end of systole and diastole, calculated from the method by Teichholz et al.;³ and (4) LV ejection fraction (LVEF), obtained from the difference between the diastolic and systolic ventricular volumes (volume ejected by systole), divided by the diastolic volume. The M-mode analysis is highly reproducible and presents high temporal resolution for the analysis of ventricles without spatial deformation.⁴ However, M-mode measurements, in general, adequately determine global systolic function only when there are no segmental changes, remodeling and/or geometric alterations of the LV.⁴ With the advent of 2D echocardiography, a greater amplitude of the LV spatial observation was acquired, allowing better analysis of the left ventricular systolic function, when compared to the one-dimensional analysis. This occurs in situations where there are changes in left ventricular geometry, such as apical aneurysm and other segmental changes resulting from coronary artery disease. The analysis of 2D left ventricular systolic function can be performed qualitatively (visual estimation) or quantitatively of LVEF. Visual estimation is highly dependent on the training of the operator, which can result in inaccuracy of reproduction of results. The quantitative method for volume and systolic function analysis of the most widespread and widely valid 2D-LV is the biplanar disc technique (modified Simpson's rule), in which the total volume is calculated based on the sum of the volumes of small cylindrical discs in apical cuts 4 and 2 LV chambers, with the intention of minimizing the effects of modifying the ventricular geometry in LVEF calculation.⁴ Normal volume and LVEF values, calculated using 2D echocardiography, show different values depending

on gender. Thus, for men, the final LV diastolic volume is between 34 and 74 mL/m², the final LV systolic volume is between 11 and 31 mL/m² and LVEF is between 52 and 72%; LV final diastolic volume is between 29 and 61 mL/m², LV final systolic volume is between 8 and 24 mL/m² and LVEF is between 54 and 74%.⁴ The 2D LVEF analysis may present inaccuracies during the shortening of LV (foreshortening) or inadequate acoustic window, and when there are coexistent geometric changes in the apical 4 and 2 LV chambers.⁴ The analysis of LV segmental contractility by 2D echocardiography represents a semiquantitative technique to assess regional systolic function, which has shown good application in clinical practice, especially for stress echocardiography (calculus of parietal motility index, which integrates analysis of ventricular wall thickening and ventricular segment contractility). Tissue Doppler, a technique used in the analysis of diastolic function, can also be used to assess global and segmental LV systolic function. The systolic velocity of the ventricular myocardium (s-wave), when measured in the region of the mitral annulus, reflects the longitudinal myocardial systolic shortening and may be reduced early in patients with diastolic dysfunction and normal ejection fraction.⁵ This method may also be useful for ventricular synchrony analysis and as a complement in stress echocardiography, although it does not allow adequate evaluation of systolic function in the apical LV segments and depends on the angle of incidence of the ultrasound beam.

3D echocardiography represented an improvement over 2D echocardiographic observation of LV function, once it does not present the limitations of the 2D analysis in ventricles with altered geometry, in addition to being more reproducible and better correlated with the gold standard provided by nuclear magnetic resonance.^{4,6-11} Most recent algorithms allow the calculation of LVEF and LV volumes in a semi-automatic way, with great correspondence with the analysis performed by nuclear magnetic resonance.¹² However, 3D echocardiography presents difficulties in relation to low temporal resolution and to the dependence on transthoracic echocardiographic image quality.⁴

The understanding and analysis of LV mechanics and systolic function can also be determined by the measurement of ventricular strain. Strain is defined as the modification of length of the myocardial segment (in %), considering the different spatial arrangements of the myocardial fibers. In this way, the longitudinal, circumferential and radial strain (for the respective longitudinal, circumferential and radial myocardial fibers) is calculated. The strain can be calculated for each of the LV segments or for all segments (global LV strain).^{13,14} The analysis of the cardiac mechanics can be performed from parameters derived from myocardial deformation, such as twist, torsion and LV rotation. In order to obtain ventricular strain, the most commonly used technique takes into account the movement of gray points in the myocardium during the cardiac cycle (speckle tracking technique).^{13,14} Global 2D strain has the advantages of not depending on the angle of the ultrasound beam (as in tissue Doppler) and of presenting an independent prognostic LVEF value.⁴ However, it does not yet present a standardized value of normality among the different manufacturers of echocardiography equipment.⁴ The LV global longitudinal strain (GLS) has been the one most

commonly used in practice, which is useful for the detection of subclinical myocardial dysfunction, even when LVEF is preserved; for example: evaluation of cardiotoxicity after the use of chemotherapy for antineoplastic treatment, rejection after heart transplantation, severe aortic stenosis, hypertrophic cardiomyopathy and myocardium infiltrative diseases.¹⁵⁻¹⁹

2.2. Left Ventricular Diastolic Function

The evaluation of LV diastolic function is an integral part of routine echocardiography analysis, especially in patients with dyspnea or suspected heart insufficiency.^{20,21} Furthermore, in several cardiopathies, the diastolic dysfunction precedes the systolic one. Diastolic dysfunction is usually the result of altered relaxation, with or without reduction of restorative forces (early diastolic suction), and increased LV stiffness, leading to elevated LV filling pressures.²⁰ When pulmonary capillary pressure exceeds 12 mmHg, or final diastolic LV pressure exceeds 16 mmHg, filling pressures are considered high.²¹ Elevation of filling pressures occurs as a compensatory response to maintain adequate cardiac output, and its estimation is important not only for the diagnosis of cardiac insufficiency but also for the definition of its severity and response to treatment.²¹ It is recommended that the non-invasive analysis of diastolic function be performed by the integrated approach of several techniques, the most important ones being: Pulsatile Doppler of the mitral flow, tissue Doppler of the mitral valve annulus, left atrial volume (LA) indexed by body surface and tricuspid regurgitation velocity.²⁰ Pulmonary venous flow and Valsalva maneuver can be used as additional parameters in specific cases, which are useful in differentiating the degrees of diastolic dysfunction.²⁰ While pulsatile and tissue Doppler velocities reflect the instantaneous filling pressures of the LV, the measurement of the LA volume reflects the cumulative effect of filling pressures over time and, therefore, this index is the chronic expression of diastolic dysfunction.²² However, it is important that other causes of LA enlargement are discarded and that this data is taken into consideration along with the patient's clinical condition, chamber size and Doppler indices for the evaluation of diastolic function.

In individuals with preserved systolic function and without structural heart disease, diastolic dysfunction is considered if there is a change of more than 50% of the following 4 parameters: relationship between the early diastolic velocity of mitral inflow (E) and the early diastolic velocity of the mitral annulus (e') $E/e' \text{ mean} > 14$; septal $e' \text{ velocity} < 7 \text{ cm/s}$ or lateral $< 10 \text{ cm/s}$; tricuspid regurgitation velocity $> 2.8 \text{ cm/s}$ and LA indexed volume $> 34 \text{ mL/m}^2$.^{20,21} For the group of patients with systolic dysfunction and those with preserved systolic function concomitant with the presence of cardiac disease (clinical or echocardiographic manifestation), the integrated use of the information allows us, in most cases, to estimate the ventricular filling pressures and the graduation of diastolic dysfunction.²⁰ Three patterns of diastolic dysfunction are defined, in ascending order of severity: grade I (abnormal ventricular relaxation without increase of filling pressures); grade II (elevation of filling pressures coexisting with altered relaxation, usually presenting "pseudonormal pattern" of the mitral flow); and grade III (very high filling pressures, accompanied by a restrictive pattern of the mitral flow). To

define the presence of increased filling pressures in this group with heart disease, we must first analyze the mitral flow, before other parameters. The relationship between E and the atrial diastolic velocity of the mitral inflow (A) $E/A \leq 0.8$ (with E-wave $\leq 50 \text{ cm/s}$) is compatible with normal filling pressures and isolated abnormal relaxation, while the relation $E/A \geq 2$ is consistent with elevated filling pressures. However, for cases with an $E/A > 0.8$ and < 2 , an abnormality of at least 2 of the following 3 parameters is required: E/e' ; tricuspid regurgitation velocity; and LA indexed volume. In some cases, the definition criteria for diastolic dysfunction are not completely fulfilled, and thus the degree of diastolic dysfunction can be reported as indeterminate.²⁰ This algorithm for the evaluation of diastolic dysfunction from the echocardiography has recently been validated in a multicenter study which assessed patients with and without left ventricular systolic dysfunction.²³ Non-invasive evaluation of filling pressures by echocardiography correlated with the diastolic pressures measured by catheterization, showing greater accuracy than isolated clinical parameters.²³

It should be noted that the parameters for evaluation of diastolic function may present important limitations in specific situations, such as hypertrophic cardiomyopathy, mitral annular calcification, severe mitral regurgitation, cardiac transplantation and cardiac arrhythmias.²⁰ Some patients, even with grade I diastolic dysfunction defined at rest, become symptomatic only during exercise and therefore it may be useful to analyze filling pressures during physical stress (diastolic stress echocardiography).^{20,24} Patients with diastolic dysfunction are unable to increase ventricular relaxation with exercise, when compared to normal subjects, with increased filling pressures, which can be identified by increased E/e' ratio and tricuspid regurgitation velocity.²⁴ In normal patients, velocities of E and e' increase proportionally and the index remains constant. Finally, the evaluation of diastolic function using techniques derived from strain and strain rate is promising, but requires further studies to establish its additional clinical value.²⁰

2.3. Cardiomyopathies

Cardiomyopathies are a heterogeneous group of myocardial diseases associated with mechanical and/or electrical dysfunction, which usually exhibit inappropriate ventricular hypertrophy or dilatation, due to a variety of causes, often genetic.²⁵ Cardiomyopathies are confined to the heart or are part of generalized systemic disorders. The classification is based on functional or structural changes in the following subtypes: dilated, hypertrophic, restrictive, and arrhythmogenic cardiomyopathy (or dysplasia) of the right ventricle (RV), more recently referred to as arrhythmogenic cardiomyopathy.²⁶ Subsequently, as the knowledge on the genetics foundations of cardiomyopathies developed, other classifications have been proposed, subdivided into genetic, acquired and mixed.²⁶ More recently, channelopathies and related disorders, such as long and short QT syndrome, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia, have been included in the group of cardiomyopathies, since they are cardiomyocyte diseases characterized by arrhythmogenic electrophysiological dysfunction.^{25,26}

Statement

2.3.1. Dilated Cardiomyopathy

It is characterized by LV dilation associated with global systolic dysfunction, in the absence of volume or pressure overload. The prevalence of dilated cardiomyopathy (DCM) is variable, reflecting the geographical and ethnic differences, as well as the methodologies used. A prevalence of 1:250 is estimated, based on the frequency of the left ventricular dysfunction as an expression of DCM.²⁷ The criterion to define LV dilation is the final diastolic diameter $> 2.7 \text{ cm/m}^2$. With increased gradual dilatation on the short axis, the LV cavity becomes spherical, with sphericity index (long/short axis dimension) close to 1 (normal value > 1.5).²⁸ Wall thickness is usually normal, but the myocardial mass is increased. The degree of impairment of systolic function is variable, and systolic dysfunction is often progressive. LV volumes are calculated in a more reproducible and accurate way by using the 3D echocardiography. Abnormalities associated with diastolic function may be present, contributing to the variation in the clinical and hemodynamic presentation of DCM. The involvement of the RV can be evidenced, but it is not a criterion for the diagnosis of DCM.²⁹ Notably, DCM is associated with an increased risk of severe arrhythmia, indicating the pathological involvement of the cardiac conduction system. Complex remodeling of one or both ventricles contributes to the secondary features of DCM, which include functional mitral and tricuspid regurgitation, enlarged atria, intracavitary thrombi, and evidence of low cardiac output.²⁸ In the context of DCM, the analysis of diastolic function aims to estimate the filling pressures; and the mitral flow pattern is usually enough to identify patients with increased LA pressure. E-wave deceleration time is an important predictor of outcomes in these patients.³⁰ Other diastolic dysfunction parameters, including the E/e' ratio, have good correlation with pulmonary capillary pressure and have an additional prognostic value for LVEF.³⁰

Echocardiography is the imaging method of choice for the evaluation of DCM patients, providing key data not only for diagnosis, risk stratification and treatment definition, but also plays a key role in the evaluation of family members.²⁸ Key echocardiography indications in the evaluation of DCM are displayed in table 1. Transthoracic echocardiography (TTE) is indicated in the initial evaluation of patients with heart failure and suspected DCM. TTE is recommended in first-degree relatives of DCM patients due to the high incidence (20 to 50%) of familial DCM.²⁸ Several echocardiographic parameters were used to assess mechanical desynchrony in patients with DCM. However, the broader role of echocardiography in the selection of patients for cardiac resynchronization therapy remains undefined. Currently, echocardiographies are limited to patients with borderline QRS duration (120 to 149 ms), whose presence of intra- or interventricular desynchrony may provide additional information.²⁸ The echocardiography guiding the placement of electrodes at the site of greater mechanical activation delay (evaluation by speckle tracking) showed benefit in heart failure free survival, with a more favorable impact on ischemic heart disease compared to DCM.³¹

2.3.2. Chagasic Dilated Cardiomyopathy

Chagasic dilated cardiomyopathy (CCM) presents similar characteristics to idiopathic DCM, but with predominance of segmental changes in contractility, especially in the basal segments of the inferior and inferolateral walls.³² Apical aneurysm is a typical CCM finding and is useful in the differential diagnosis of dilated cardiomyopathies.³³ The morphology of aneurysms is variable and non-standard sections are often required for the identification of apical contractile changes. The presence of thrombi within the aneurysms is frequent and associated with cerebral thromboembolic events.³⁴ Diastolic dysfunction is universally present in patients with CCM and heart failure.³⁵ The main echocardiographic parameters previously studied with a prognostic value in CCM are LVEF, right ventricular function, LA volume and E/e' ratio.^{33,36} The contractile function of the LA evaluated by the negative peak of the global atrial strain was an independent predictor of clinical events in the CCM.³⁵ The heterogeneity of systolic contraction, quantified by mechanical dispersion to speckle tracking, was associated with ventricular arrhythmias in patients with CCM, regardless of LVEF.³⁷ Recommendations for performing TTE in CCM are set out in table 1.³⁸

2.3.3. Cardiac Resynchronization Therapy and Pacemaker Optimization

Cardiac resynchronization therapy is an established treatment option for patients with heart failure with marked reduction of LVEF. The echocardiography is fundamental in the indication, estimation of success and evaluation of the results of this procedure and may also contribute to the recovery of unfavorable results. This treatment is indicated as class I in patients with heart failure (New York Heart Association (NYHA) functional class II, III or IV), with LVEF lower than 35%, optimized medication and left bundle branch block with QRS duration above 150 ms.²⁸ Also in class IIa and IIb indications, it is necessary to recognize the reduction of the LVEF below 35%, being contraindicated when this value is not present. Therefore, in the possibility of indication for cardiac resynchronization therapy, transthoracic echocardiography is a class I indication, level of evidence C. In this examination, it is mandatory that LVEF be obtained by the Simpson 2D method, with a description, in the report, of their volumes. It is also possible to use the 3D methodology, of less variability, although still unproven in this clinical scenario. Approximately 30% of patients do not present clinical improvement or significant reduction in LV final systolic volume.³⁹ TTE can provide information that helps identify a greater probability of successful treatment response, such as the presence of mechanical, inter- and intraventricular desynchrony, the presence of myocardial reserve and determination of the last site of activation, which may be associated with higher degree of fibrosis. To this end, the use of a variety of methods is encouraged, from the visual evaluation of 2D echocardiography, M-mode,⁴⁰ tissue Doppler and, especially, the use of a technique that evaluates longitudinal⁴¹ or radial myocardial deformation.^{42,43} In the evaluation of successful response to treatment, it is expected, in regards to imaging, mainly negative remodeling to be observed, usually characterized by reduction of 15% of the

Table 1 – Recommendation of echocardiographies in dilated cardiomyopathies

Recommendation	Class of recommendation	Level of evidence
Assessment of patients with suspected dilated cardiomyopathy or heart failure	I	C
Assessment of signs and symptoms suggestive of myocardial dysfunction	I	C
Reassessment of patients with cardiomyopathy known to present worsening of symptoms or to require changes in therapy	I	C
First-degree relatives of patients with dilated cardiomyopathy	I	B
Assessment of candidate patients for cardiac resynchronization therapy with LBBB and QRS duration between 120 and 149 ms	IIa	C
Reassessment of routine in patients with stable dilated cardiomyopathy, without clinical or therapeutic changes	III	C
Chagasic cardiomyopathy		
Initial evaluation of patients with positive serology for Chagas disease for diagnosis and risk stratification of cardiomyopathy	I	C
Patients with the indeterminate form of Chagas disease who present new electrocardiographic alterations compatible with the development of cardiomyopathy	I	C
Patients who present worsening symptoms of heart failure, syncope, arrhythmic or thromboembolic events	I	C
Routine reassessment of clinically stable patients with no changes in therapy	III	C

LBBB: left bundle branch block.

initial systolic volume, analyzed between 3 and 6 months of the implant.^{39,44} In case the negative remodeling and/or the clinical improvement of the patient is not met, one possibility is to adjust the pacemaker, guided by TTE, to optimize the atrial and ventricular stimulus intervals. The main correction in this case seems to be adjustment of the atrial and ventricular stimulus intervals, guided by the echocardiography, which allows for retrieval of the results.^{45,46}

2.3.4. Assessment after Heart Transplantation

The echocardiography is the main noninvasive imaging modality as well as the most versatile one in the evaluation and monitoring of patients after cardiac transplantation, providing accurate information on morphology and graft function. From the immediate postoperative period up to the moment of hospital discharge, serial echocardiographic exams are recommended both to identify and monitor surgical complications and early graft dysfunction, whether due to primary or secondary causes (e.g., reperfusion injury, non-responsive pulmonary hypertension (class I, level B)).^{47,48} In the presence of early graft dysfunction, the echocardiography usually shows an overall reduction in myocardial function (LVEF < 45%), loss of the contractile reserve, increase in RV volume with systolic dysfunction (tricuspid annular plane systolic excursion – TAPSE < 15 mm or RV ejection fraction < 45%).⁴⁷ A comprehensive echocardiographic examination (class I, level B) is recommended in the sixth month after cardiac transplantation, which will serve as the baseline for assessing graft morphology and function during sequential and regular follow-up examinations (interval and frequency of exams in figure 1).⁴⁷ Quantifications of cardiac chambers size and volumes, RV systolic function, LV diastolic and systolic parameters, and pulmonary arterial

pressure should be performed on the sixth month and subsequent echocardiographies.⁴⁷ It is recommended that such echocardiographic studies also include advanced methodologies, such as the study of myocardial deformation (strain) and 3D evaluation of the volumes and function of cardiac chambers and tricuspid valve (frequently injured during the endomyocardial biopsy procedure), for providing a more accurate and comprehensive analysis (class I, level B).⁴⁷

It should be noted that there is no single isolated echocardiographic parameter that can be reliably used to diagnose acute rejection.⁴⁷ However, an echocardiographic study with no change from the baseline study has a high negative predictive value for acute rejection of the graft. On the other hand, if several echocardiographic parameters are abnormal, the probability of acute rejection of the graft increases considerably.⁴⁷ When an abnormality is detected, a careful review of the images of the present study and the baseline study (side-by-side) is highly recommended (class I, level B).⁴⁷ GLS is an adequate parameter to assist in the subclinical diagnosis of graft dysfunction, regardless of etiology, in addition to an adverse event predictor, when comparing the variations of values occurred during serial evaluations (class IIb, level B).^{47,49,50} The association of GLS with endomyocardial biopsy helps to characterize and monitor an episode of acute rejection or global dysfunction.⁴⁷ Pericardial effusion should be serially assessed for extent, location and hemodynamic impact (class IIb, level B). In the case of a recently detected pericardial effusion, the hypothesis of acute rejection should be considered, taking into account the patient's global and clinical echocardiographic evaluation.^{47,51} Cardiac graft vascular disease is the main cause of late complication; and the dobutamine stress echocardiography has proven to be a safe and accurate method to identify the affected patients.^{47,52-54}

Statement

The evaluation of the coronary reserve flow, as well as the sonographic contrast infusion to highlight the borders and to evaluate the myocardial perfusion, when combined with stress echocardiography, have been shown to increase the accuracy of the diagnosis of graft vascular disease.⁵⁵⁻⁵⁹ Thus, dobutamine stress echocardiography alone (class IIA, level B) or in association with the evaluation of the flow of coronary reserve and/or with the use of sonographic contrast (class I, level B) may be an adequate noninvasive alternative to routine coronary angiography to assess the presence of cardiac graft vasculopathy, provided that the medical center has good experience with methodologies.

In addition to the role of cardiac graft monitoring, intraoperative echocardiography can be used as an alternative to fluoroscopy to guide endomyocardial biopsies, avoiding repeated exposure to X-rays, particularly in children and young women (class I, level B). Whether in transthoracic or transesophageal mode, the echocardiography allows a simultaneous visualization of the soft tissues and the biotope, guaranteeing greater biopsy safety in different regions of the RV with a reduction in the complication rate.^{47,60} Furthermore, the use of echocardiography during the procedure allows immediate recognition and management of a possible complication.

2.3.5. Monitoring of Cardiac Function During Chemotherapy with Cardiotoxic Drugs

Current cancer therapy is quite effective in some types of tumors, though it can induce cardiovascular complications. Cardiotoxicity (CT) induced by cancer treatment is recognized as the major cause of morbidity and mortality in cancer survivors.⁶¹ Before starting anti-neoplastic treatment, it is essential to assess the risk of CT,⁶² taking into consideration: (a) the specific risk of the drug used in chemotherapy, as some of them may affect the cardiac function (anthracyclines, trastuzumab), while other ones, the vascular function (5-fluoracil, capecitabine), or both (bevacizumab); (b) the use of radiotherapy, as it increases the risk of heart failure when concomitant with anthracyclines, pericardial lesion (constrictive pericarditis) and coronary artery disease; (c) the presence of previous risk factors, such as age > 65 years, female gender, hypertension, diabetes mellitus, coronary artery disease and history of heart failure. All patients receiving potentially cardiotoxic drugs should be periodically monitored for CT signs, which can be classified according to the injury the drug used produces.⁶³ CT Type I, potentially irreversible, anthracycline-related dose, is dose-dependent, mainly at > 250 to 300 mg/m² (often used in the treatment of breast cancer, lymphoma, leukemia, and sarcoma). It most commonly occurs in the first year of chemotherapy, or even two to three decades after completion of treatment, as progressive systolic dysfunction. It may rarely present as an acute systolic dysfunction, immediately after dosing. Type II CT, which is potentially reversible, mainly related to trastuzumab (used in the treatment of breast cancer in patients with increased HER2 receptor expression), has no relation to the cumulative dose.⁶³ Such information is the basis for the algorithms of serial left ventricular function monitoring during and after treatment of cancer patients, published by the European Association of Cardiovascular Imaging (EACVI) and

the American Society of Echocardiography (ASE).³ The most historically used parameter is LVEF, calculated by TTE using the Simpson biplanar 2D method.⁴ LVEF values between 53 and 73% should be considered normal in the evaluation. The main advantages of 2D TTE in relation to other imaging modalities, such as radioisotope ventriculography and magnetic resonance imaging (MRI), are: greater availability, lower cost, possibility of serial re-evaluations and greater safety (absence of radiation and limitation in patients with renal insufficiency). 3D TTE, used in sequential and comparative MRI evaluations for LVEF assessment, showed reproducibility comparable to MRI and better accuracy than 2D TTE,⁶⁴ being more indicated, when available, in the serial evaluation of these patients.⁶⁵

The definition of CT due to chemotherapy was defined by the consensus of these two societies³ as the decrease of LVEF > 10 percentage points to values < 53% and should be confirmed after 2 to 3 weeks of diagnosis by new imaging. This decrease may or may not be accompanied by symptoms of heart failure and may or may not be reversible. One of the major limitations of the use of LVEF for CT diagnosis in the follow-up of these patients is that changes in LVEF occur later. In order to minimize the risk of developing irreversible cardiomyopathy, it is essential to identify early signs of CT, since the administration of cardioprotective medication in this phase may result in an improvement in cardiac function.⁶⁶ Thus, the search for a technique that allows subclinical and early detection of CT before LVEF decrease or the onset of clinical symptoms has been an area of intense investigation. In this scenario, the use of GLS gained importance, evaluating myocardial deformation. Such technique has inter- and intraobserver reproducibilities smaller than the LVEF obtained by the 2D TTE, but is limited by the variability of normal values according to the brand of the equipment used, age and gender of the patients.⁶⁷ Systematic review confirmed the prognostic value of the alterations in GLS for CT, preceding the LVEF decrease obtained by 2D or 3D TTE.¹⁵ The consensus recommends serial GLS evaluation in patients at risk of CT, with subclinical left ventricular dysfunction suggestive of a fall of > 15% of the baseline value, even without LVEF change.⁶³ The relative decrease between 8 and 15% suggests a more rigorous follow-up. GLS Variation of < 8% is consistent with absence of subclinical dysfunction.⁶³ Although some studies have drawn attention to changes in diastolic function following chemotherapy,⁶⁸ there is no current evidence to support such parameters as indicative of CT.⁶³ A use of biomarkers in the assessment integrated with imaging methods in chemotherapy patients evidenced the importance of troponin I (TnI) with a high negative predictive value in the detection of CT.⁶⁹ It is probable that patients who do not evolve with TnI elevation have lower probability of events and perhaps less need for imaging tests in subsequent evaluations.^{69,70} There is still no robust scientific evidence based on randomized clinical trials to support the algorithms proposed by the European Society of Oncology⁷¹ and the consensus of EACVI and ASE,⁶³ in the follow-up of these patients; however, these documents represent current knowledge in the area. The orientation of the EACVI - ASE consensus⁶³ to the present moment is:

a) Initial evaluation of left ventricular function before the start of chemotherapy in patients who will use potentially

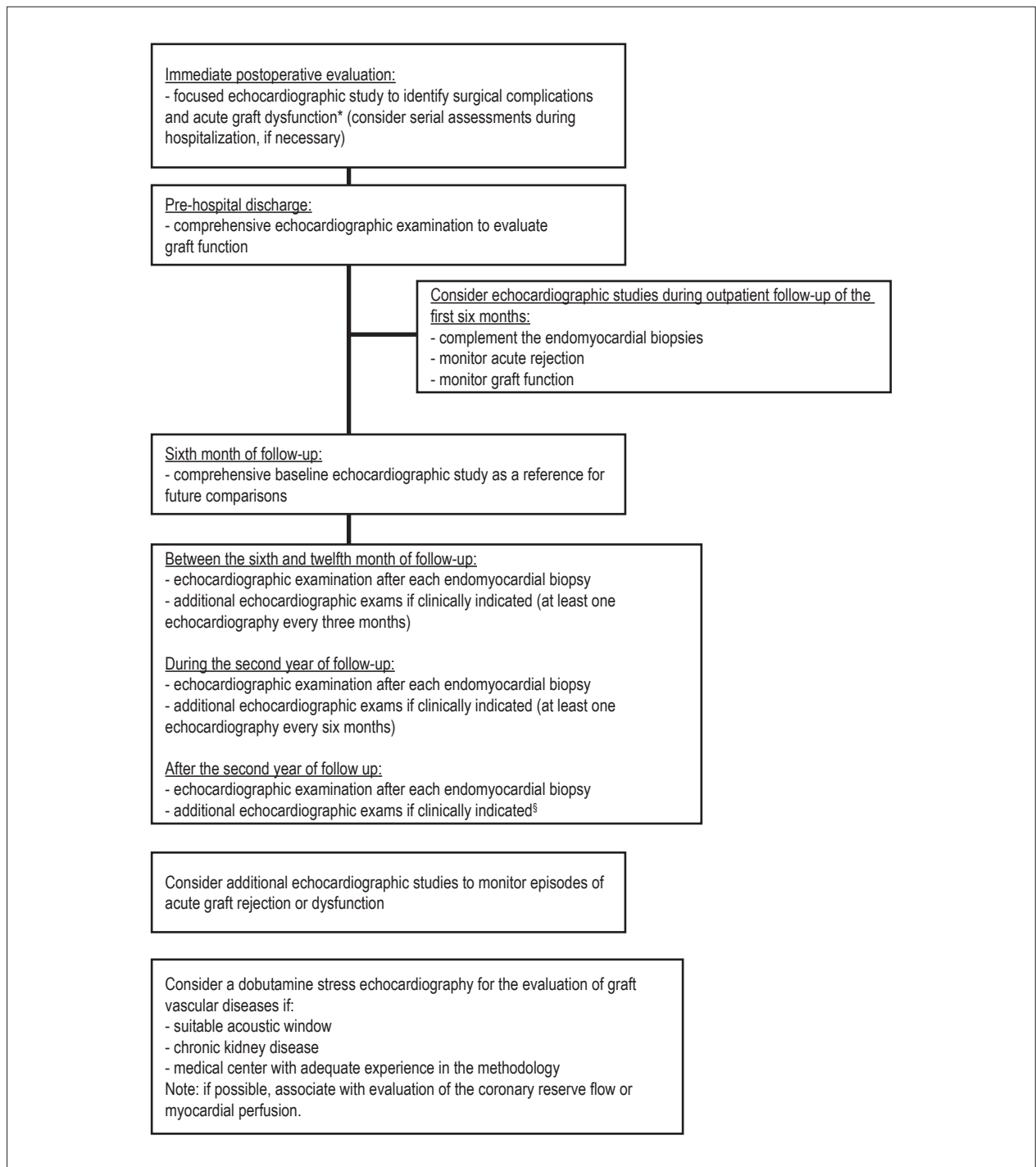


Figure 1 – Echocardiographic evaluation after cardiac transplantation.

*Graft dysfunction: confirmed on echocardiographic examination by dropping the ejection fraction by more than 10% to a value lower than 50%, compared to the baseline examination of the sixth month; [§]patients with graft dysfunction suspected or confirmed; clinical symptoms of a possible new cardiac abnormality; alterations in the resting electrocardiogram.

cardiotoxic chemotherapeutics. If it is not possible in all patients, it is recommended in those at high risk for the development of CT: age > 65 years, previous left ventricular

dysfunction, predicted use of high doses of anthracyclines (type I) or combination of type I and II drugs. To perform the LVEF assessment by the 3D TTE if available or, alternatively,

Statement

by the 2D TTE (Simpson method). It is desirable that the evaluation by GLS and TnI is carried out. If not possible to perform GLS, report the S-wave of the medial and lateral tissue Doppler of the mitral annulus. Further monitoring of left ventricular function is recommended after this initial evaluation, depending on the chemotherapy to be initiated.

b) Type I drugs (anthracyclines): evaluate left ventricular function (2D/3D LVEF and GLS) at the end of chemotherapy and after 6 months at dose < 240 mg/m². For doses > 240 mg/m², evaluate left ventricular function before each additional 50 mg/m² cycle at the end of chemotherapy and after 6 months.

c) Type II drugs (trastuzumab): evaluate left ventricular function every three months during chemotherapy.

d) Patients receiving trastuzumab following anthracycline treatment: assess left ventricular function every three months during chemotherapy and six months after its completion.

2.3.6. Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a genetic cardiovascular disease characterized by increased left ventricular wall thickness ≥ 15 mm in adults, with non-dilated ventricular cavity not explained by abnormal loading conditions, such as arterial hypertension or valve aortic stenosis.⁷² Minor hypertrophy degrees (13 to 14 mm) may also diagnose HCM, particularly among relatives of these patients. TTE is considered the initial imaging for diagnosis, stratification of the risk of cardiac events and management of patients with HCM. Among the parameters to be evaluated in HCM are: location and hypertrophy degree; identification of obstruction and intraventricular gradient at rest or intentionally caused; presence of magnitude of mitral reflux; systolic and diastolic function; and LA size. Any hypertrophy pattern may be found, though the asymmetric is the most frequent one (75% of cases), and it is more common at the confluence of the anterior interventricular septum with the LV free wall.⁷³ Other forms of hypertrophy are: basal, concentric, apical and lateral wall. There is a linear association between maximum myocardial thickness and sudden death, with greater risk in patients with thickness ≥ 30 mm.^{72,74} Gradual identification of the LV outflow tract is important in the management of symptoms and in the stratification of the risk of sudden death.⁷² TTE evaluation generally characterizes the presence of LV outflow tract obstruction (instantaneous gradient ≥ 30 mmHg) at rest (one third of patients) or after provocative maneuvers (one third), such as exercises (echocardiography under physical stress) or Valsalva maneuver. Echocardiography under physical stress can be very useful in patients with HCM, since in addition to detecting the presence and degree of obstruction during effort, it allows the objective evaluation of symptoms, functional capacity, systolic blood pressure response and the presence of secondary mitral regurgitation. Approximately 25% of HCM patients have abnormal blood pressure response during exercise, characterized by a drop in systolic pressure or by failure to increase in > 20 mmHg. This finding has been interpreted as a risk factor for unfavorable prognosis and sudden death.⁷⁵ Stress echocardiography with dobutamine is

not recommended. The cut-off value of the intraventricular gradient ≥ 50 mmHg at rest or after provocative maneuvers is considered when indicating surgical treatment or percutaneous intervention in symptomatic patients, despite therapy with optimized medication.⁷² Patients with HCM in general have diastolic dysfunction, commonly with altered relaxation (grade I), though without significant correlation between mitral flow data and LV filling pressures. Thus, the integrated approach of mitral Doppler data, tissue Doppler, pulmonary vein flow and LA volume is recommended in these patients.⁷⁶ LVEF is normal or increased in most patients, giving the false impression of preserved systolic function. However, longitudinal strain assessment invariably shows a global and regional decrease (coincident with sites of greater hypertrophy) of contractility.⁷⁷ Estimating the size of the LA is fundamental, as there is a significant correlation between the dilation of the chamber and an increased risk of cardiovascular events, such as atrial fibrillation and sudden death. The main complication of HCM is sudden cardiac death (SCD), especially in young and apparently healthy individuals.^{78,79} Cardiac defibrillator implantation for primary or secondary prophylaxis may reduce mortality from this complication and is the only therapy with evidence of life-saving potential.⁸⁰ TTE has a relevant role in the two most commonly used risk stratification scores for SCD in HCM, which determined the relationship between some clinical risk factors and prognosis. In the American model of primary prevention, one of the risk factors among 5 variables is the presence of interventricular septum thickness ≥ 30 mm.⁷⁵ In the European model, of the seven variables analyzed, three of them are provided by TTE: septum thickness, LA and left ventricular outflow tract (LVOT) gradient at rest or after Valsalva maneuver.⁷² Family screening of first-degree relatives of HCM subjects should be performed periodically due to their risk of developing the disease. Recommendations for the use of echocardiography in HCM are summarized in table 2.

2.3.7. Restrictive Cardiomyopathies

Restrictive cardiomyopathies (RCM) are a group of entities characterized by abnormalities in the ventricular filling pattern, which may be associated with thickened and rigid walls and generally preserved systolic function. RCMs comprise various entities, including, endomyocardial fibrosis (EMF), endomyocardial fibroelastosis, Löeffler parietal endocarditis, infiltrative (such as amyloidosis and sarcoidosis), storage (such as hemochromatosis and Fabry disease), idiopathic and other forms secondary to different processes (scleroderma, carcinoid syndrome, metastases of systemic neoplasms, anthracycline toxicity and irradiation heart disease).⁸¹ Diagnosis by echocardiography is based on common anatomical and functional changes: ventricular cavities of normal or reduced size, usually with Doppler degree III diastolic function (restrictive type), generally preserved overall systolic function, and dilated atria. Tissue Doppler analysis shows velocity e' obtained in the septal mitral annulus usually below 7.0 cm/s, a useful measure in constrictive pericarditis differentiation.⁸² In amyloidosis, there is thickening of the atrioventricular valves, myocardial walls, and eventually the atrial septum, with a more intense

Table 2 – Recommendations of transthoracic echocardiography, echocardiography under physical stress and transesophageal echocardiography in hypertrophic cardiomyopathy^{72,75}

Recommendation	Class of recommendation	Level of evidence
TTE in the initial assessment of all patients with suspected HCM, at rest and during Valsalva maneuver	I	B
EPS in symptomatic patients with resting or Valsalva intraventricular gradient < 50 mmHg to assess the degree of dynamic obstruction and mitral regurgitation during exercise	I	B
Reassessment by TTE when there are changes in symptoms or a new cardiovascular event	I	B
TTE in the assessment of therapeutic results of pharmacological, surgical (myectomy), interventional (alcoholic septal artery occlusion) and pacemaker treatments	I	C
TTE in the screening of first-degree relatives with HCM diagnosis	I	B
Serial TTE (every 12 to 18 months) in children of HCM patients, starting at age 12 (or earlier, if there is intention to take on competitive sports or sudden death among relatives)	I	C
TTE during alcohol septal artery ablation	I	B
TEE in intraoperative myectomy monitoring and during alcoholic occlusion of the septal artery with inadequate TTE	I	B
Serial TTE every one to two years may be useful in stable symptomatic patients to reassess myocardial hypertrophy, dynamic obstruction, and ventricular function	IIa	C
TEE may be useful when TTE is inconclusive, in the planning of myectomy or in the evaluation of mitral regurgitation secondary to mitral valve abnormalities	IIa	C
Serial TTE (every five years) is reasonable in periodic reassessment in first-degree relatives of adult HCM patients	IIa	C
TTE combined with intravenous contrast injection is reasonable if the diagnosis of apical HCM and/or apical infarction are doubtful, or the quantification of hypertrophy is inadequate, especially if MRI is unavailable, non-diagnostic or contraindicated	IIa	C
EPS may be useful in asymptomatic HC patients, with no dynamic obstruction at rest when gradient detection in LVOT is relevant for lifestyle or career change orientation, or decision making on medical treatment	IIb	C
TTE should not be performed in less than 12 months in HCM patients when there is no change in symptoms or predicted conduct change	III	C

TTE: transthoracic echocardiography; HCM: hypertrophic cardiomyopathy; EPS: echocardiography under physical stress; TEE: transesophageal echocardiography; LVOT: left ventricular outflow tract.

(ecorrefringence) reflection and “granular and sparkling” myocardial aspect.⁸³ The GLS analysis of the LV with 2D echocardiography in amyloidosis observes very low values, especially in the mid and basal segments with relative “apical sparing” (it aids in the differential diagnosis with other diseases).⁸⁴ In EMF, one may observe: obliteration of the apex by fibrosis, signs of ventricular restriction, and involvement of the atrioventricular valves. The fibrosis of the apical thrombi is differentiated due to absence of akinesia or dyskinesia in the left EMF. Another differential diagnosis is apical HCM, which presents no endocardial thickening or restrictive pattern and displays specific electrocardiographic changes. Cardiac sarcoidosis may present with regional contractile abnormalities and non-ischemic distribution aneurysms. GLS measure represents an early marker of myocardial involvement in sarcoidosis and the magnitude of the reduction is associated with poor prognosis.⁸⁵ The recommendations for TTE in RCM are set out in table 3. Transesophageal echocardiography (TEE) is indicated when there are technical difficulties to TTE and in the transoperative monitoring of fibrosis and apical correction of valve defects.

2.3.8. Arrhythmogenic Cardiomyopathy (Right Ventricle Arrhythmogenic Dysplasia)

Arrhythmogenic cardiomyopathy (AC) is considered an inherited cardiomyopathy with autosomal dominant transmission, predisposing to the emergence of ventricular arrhythmias, sudden death in young people, ventricular dysfunction and heart failure. Due to the frequent involvement of the LV, the use of the term CA is currently recommended, which comprises both ventricles, replacing the term “arrhythmogenic dysplasia of the RV”.⁸⁶ The disease is characterized by a progressive replacement of the ventricular myocardium by fibrous and adipose tissue, which can lead to thinning of the wall and aneurysm formation. In the RV, the process is typically located in the inferior, apical and infundibular walls (dysplasia triangle), and may be diffuse or segmental. LV involvement occurs in more than half of the cases, typically located in the subepicardium or mesocardium, and often confined to the inferolateral segment. Echocardiography is the imaging modality of choice in the initial assessment of AC (Table 4) and the most commonly used propaedeutic method for patient follow-up.⁸⁷ Typical morphologic features in patients with CA include regional

Statement

Table 3 – Recommendations of echocardiography in restrictive cardiomyopathies

Recommendation	Class of recommendation	Level of evidence
Diagnostic investigation of patients with heart failure without clear etiology	I	C
Differential diagnosis of patients with restrictive syndrome	I	C
Symptomatic patients with systemic diseases potentially causing RCM	I	C
Patients with hypereosinophilic syndrome, ascites and distended jugular veins	I	C
Patients with ascites and lower limb edema, without established diagnosis	I	C
Patients submitted to radiotherapy with signs of systemic venous hypertension	I	C
Reassessment of patients with previous RCM diagnosis when there is a change in the clinical course of the disease	I	C
Patients with EMF for therapeutic planning and prognostic evaluation	IIa	C
Patients with edema and ascites, with evidence of normal systemic venous pressure and no evidence of cardiopathy	III	C

RCM: restrictive cardiomyopathies; EMF: endomyocardial fibrosis.

contractile abnormalities and/or dilation and right ventricular dysfunction. Among the traditional echocardiographic criteria, derived from 2D echocardiography, proposed for the diagnosis of AC,⁸⁸ are: presence of akinesia, dyskinesia or right ventricular aneurysm; increased ventricular outflow tract diameter (measured on long and short parasternal axis); and reduction of the fractional variation of the RV area. Recently, the routine and systematic addition of other echocardiographic measurements and techniques was recommended in order to improve evaluation:⁸⁹

- Conventional parameters: basal RV diameter (normal ≤ 41 mm); systolic excursion of the annular tricuspid plane (TAPSE – normal ≥ 17 mm).

- Advanced parameters: wave s' to the tissue Doppler of the RV's free wall (normal ≥ 9.5 cm/s); longitudinal strain of the RV's free wall (normal $\geq -20\%$); LV's GLS (normal $\geq -18\%$); RV ejection fraction to 3D echocardiography (normal $\geq 45\%$).

In short, TTE, preferably with analysis of conventional and advanced parameters, is indicated in patients with suspected or established AC (evaluation of disease progression), as well as in family screening of first-degree relatives.

2.3.9. Non-compaction Cardiomyopathy

Non-compaction cardiomyopathy (NCC) is considered a distinct cardiomyopathy, marked by genetic heterogeneity, with an overlapping of different phenotypes and great

variability of clinical presentation. As a consequence, there is still controversy in the literature regarding its nomenclature: whereas for the American Heart Association (AHA)⁹⁰ it is considered a primary cardiomyopathy, the European Society of Cardiology (ESC)⁸¹ considers it an unclassified disorder. Its pathogenesis implies early interruption of compaction of the trabecular meshwork of the LV during embryogenesis, resulting in the formation of two layers: a thin compacted epicardial layer and a thick endocardial one (similar to a “spongy” mesh) with marked trabeculations and deep intertrabecular recesses. The 2D echocardiography is the basis for diagnosis, follow-up, and better delineation of NCC phenotypic expressions.⁹¹ Several criteria have been employed in diagnosis, taking into account the increase in the proportion of the non compacted layer (for example, the non compacted/compacted ratio at the end of systole > 2), presence of excessive trabeculation, hypokinesia of non compacted areas (commonly located at the apex and lateral wall) and visualization of flow in the recess (via color Doppler). New techniques have recently been incorporated to aid in diagnosis, such as the use of echocardiographic contrast, 3D echocardiography and myocardial strain for the analysis of regional deformation and rotation (which assumes a characteristic pattern in this nosological entity).⁹² Therefore, it should be noted that the diagnosis of suspected cases has increased in recent years, due to advances and improvements in imaging methods, as well as the

Table 4 – Recommendations of the echocardiography in arrhythmogenic cardiomyopathy

Recommendation	Class of recommendation	Level of evidence
Assessment of patients with suspected AC	I	B
Reassessment of patients with known AC when there is change of symptoms or new cardiovascular event	I	C
Family screening in first-degree relatives of AC patients	I	C
Routine re-evaluation of clinically stable patients with no changes in therapy	III	C

AC: arrhythmogenic cardiomyopathy.

perception of the need to actively investigate first-degree relatives affected by the disease (described in 13 to 50% of this specific group).⁹³ On the other hand, increasingly frequent “exam findings” (physiological versus pathological variants) have been reported in clinical practice, leading to the worrisome excess of diagnoses.⁷ Therefore, it is recommended to carry out a comprehensive evaluation, including clinical, electrocardiographic data and careful analysis of the findings in complementary imaging studies.⁹⁴ The recommendations for performing the echocardiography in NCC are set out in table 5.

2.4. Arterial Hypertension and Myocardial Hypertrophy

The elevation of systolic stress in the LV wall, secondary to systemic arterial hypertension (SAH), can produce myocardial hypertrophy by increasing ventricular mass.⁹⁵ Unlike physiological hypertrophy (growth, pregnancy and physical activity), characterized by preserved cardiac structure and function, left ventricular hypertrophy (LVH), secondary to SAH, is commonly associated with fibrosis,

myocardial dysfunction and increased mortality.⁹⁶ The echocardiography is the clinical choice exam to detect LVH, due to its being more accurate than the electrocardiogram^{97,98} and allowing estimation of LV mass (LVM). The methodology to measure LVM and to define its cut-off points and index form (body surface, height, weight) varies between studies. Most echocardiography authors and laboratories follow the recommendations published by ASE and EACVI.^{95,99} LVM indexing to the body surface area in g/m² is the most used one,¹⁰⁰ and normality values are different for men and women (Table 6).^{95,99}

Cumulative exposure to elevated blood pressure levels among young adults is associated with LV systolic dysfunction in mid-life.¹⁰¹ The presence of LVH is considered as evidence of target organ damage in hypertensive patients, and its association with cardiovascular diseases and mortality is well documented.¹⁰²⁻¹⁰⁴ Such an increase in cardiovascular risk in hypertensive patients is directly related to LVM, regardless of blood pressure values.¹⁰³ In addition to LVM, the geometric pattern of LVH is also seen as an important variable related

Table 5 – Recommendations of echocardiography in non-compaction cardiomyopathy

Recommendation	Class of recommendation	Level of evidence
NCC clinical suspicion	I	C
Reassessment of patients with known NCC when there is change of symptoms or new cardiovascular event	I	C
Screening in first-degree relatives of NCC patients	I	C
Carriers of muscular diseases and/or other clinical syndromes that may be related	I	C
Use of new techniques such as strain, 3D echocardiography and echocardiographic contrast for complementary evaluation and aid in differential diagnosis	Ila	B
Routine reassessment of clinically stable patients with no change in therapy	III	C

NCC: non-compaction cardiomyopathy.

Table 6 – Degree of abnormalities of left ventricular mass^{95,99}

Linear method	Female				Male			
	Normal	Slight increase	Moderate increase	Severe increase	Normal	Mild increase	Moderate increase	Severe increase
LV mass, g	67 to 162	163 to 186	187 to 210	≥ 211	88 to 224	225 to 258	259 to 292	≥ 293
Mass/BS, g/m ²	43 to 95	96 to 108	109 to 121	≥ 122	49 to 115	116 to 131	132 to 148	≥ 149
Mass/height, g/m	41 to 99	100 to 115	116 to 128	≥ 129	52 to 126	127 to 144	145 to 162	≥ 163
Mass/height ^{2.7} , g/m ^{2.7}	18 to 44	45 to 51	52 to 58	≥ 59	20 to 48	49 to 55	56 to 63	≥ 64
RWT (2 x LVPW/LVDD)	0.22 to 0.42	0.43 to 0.47	0.48 to 0.52	≥ 0.53	0.24 to 0.42	0.43 to 0.46	0.47 to 0.51	≥ 0.52
Septum thickness, cm	0.6 to 0.9	1.0 to 1.2	1.3 to 1.5	≥ 1.6	0.6 to 1.0	1.1 to 1.3	1.4 to 1.6	≥ 1.7
LVPW thickness, cm	0.6 to 0.9	1.0 to 1.2	1.3 to 1.5	≥ 1.6	0.6 to 1.0	1.1 to 1.3	1.4 to 1.6	≥ 1.7
2D Method								
LV mass, g	66 to 150	151 to 171	172 to 182	≥ 193	96 to 200	201 to 227	228 to 254	≥ 255
Mass/BS, g/m ²	44 to 88	89 to 100	101 to 112	≥ 113	50 to 102	103 to 116	117 to 130	≥ 131

LV: left ventricle; BS: body surface; RWT: relative wall thickness; LVPW: left ventricle posterior wall; LVDD: left ventricle diastolic diameter; 2D: two-dimensional.

Statement

to cardiovascular risk. Four patterns of LV geometry⁹⁹ are described in (Table 7). The altered geometric patterns (concentric LVH, eccentric LVH and concentric remodeling) are predictors of cardiovascular complications in hypertensive patients, with concentric LVH being associated with higher risk of events.¹⁰³

Another frequent finding in SAH is the presence of LV diastolic dysfunction.¹⁰¹ Hypertensive individuals with heart failure commonly present with LVH, abnormalities in diastolic function and preserved ejection fraction. In these cases, diastolic dysfunction alone may be responsible for the signs and symptoms of heart failure.¹⁰⁵ In addition, E/e' ratio > 13 is associated with high cardiac risk in hypertensive patients, regardless of LVM.¹⁰⁶ The use of GLS, obtained by 2D speckle tracking, allows for the early identification of subclinical systolic dysfunction in several scenarios, including hypertensive patients without LVH.¹⁰⁷ GLS decline was related to hospitalization by heart failure, infarction, stroke, and death in patients with asymptomatic hypertensive heart disease.¹⁰⁸ The regression of LVH in hypertensive patients, evaluated by serial echocardiographies after therapeutic interventions, is associated with decreased risk of fatal and non-fatal

cardiovascular events, even in those cases where LVH has not been detected by the electrocardiogram.¹⁰⁹ This benefit is directly related to the degree of reduction of LVM indexed to body surface, regardless of ambulatory blood pressure. LVH regression is also associated with an improvement in LV systolic¹¹⁰ and diastolic function¹¹¹ in hypertensive patients. The thoracic aorta is more frequently affected by dilatation in hypertensive patients without adequate blood pressure control than in normotensive and controlled hypertensive ones.¹¹² Long-term follow-up has shown that blood pressure levels are one of the main modifiable factors of adult aortic root dilatation.¹¹³ The recommendations for performing the echocardiography in SAH are listed in table 8.

2.5. Athletes

The clinical entity called “athlete’s heart” has been recognized for more than two decades¹¹⁴ and is characterized by cardiac morphological alterations, mainly of increased ventricular mass, secondary to physical training stimulus. These alterations are not accompanied by changes in myocardial function, not only by conventional echocardiographic methods but also by techniques such as tissue Doppler and strain.^{115,116} Still, as a result of intact ventricular function, there is no significant increase in atrial cavities¹¹⁷ and reversibility of morphological alterations after discontinuation of training may be a decisive diagnostic factor in doubtful cases. The use of TTE, therefore, can elucidate cases of doubtful diagnosis between this situation and hypertrophies or pathological ventricular remodeling, such as HCM or even hypertrophy secondary to SAH.¹¹⁵ However, the use of echocardiography as a routine method in the follow-up of athletes lacks robust scientific evidence.

Events of sudden death in athletes constitute an important clinical scenario and the potential prevention of some situations through clinical cardiological evaluation raises the discussion about the need to use complementary methods in this evaluation. Although not all deaths in athletes are cardiovascular, pathologies such as hypertrophic cardiomyopathy and coronary anomalies are among the

Table 7 – Geometric patterns of the left ventricle⁹⁹

Left ventricle geometry	Left ventricle mass / body surface (g/m ²)	Left ventricle mass /body surface (g/m ²)
Normal	≤ 115 (men) or ≤ 95 (women)	≤ 0.42
Concentric hypertrophy	> 115 (men) or > 95 (women)	> 0.42
Eccentric hypertrophy	> 115 (men) or > 95 (women)	≤ 0.42
Concentric remodeling	≤ 115 (men) or ≤ 95 (women)	> 0.42

**Measures taken by the linear method.*

Table 8 – Recommendations of the echocardiography in the evaluation of hypertensive patients

Recommendation	Class of recommendation	Level of evidence
LVH detection	I	A
Assessment of systolic and diastolic function in hypertensive patients with clinical suspicion of heart failure	I	A
Hypertensive patients with left bundle branch block	I	C
Assessment of the aortic diameter in hypertension without adequate blood pressure control	I	B
Hypertensive patients with LVH on ECG for quantification of LVH and definition of LV geometric pattern	IIa	B
Global longitudinal strain evaluation in patients with hypertensive cardiopathy	IIa	C
Reassessment of patients with hypertensive heart disease without alteration of their clinical status	IIb	B
Assessment of first-degree relatives of hypertensive patients	III	C
Selection of antihypertensive therapy	III	C
Monitoring of antihypertensive therapy in controlled and asymptomatic individuals	III	C

LVH: left ventricular hypertrophy; ECG: electrocardiogram; LV: left ventricle.

most frequent causes of sudden death during exertion in this population.^{118,119} Although the usefulness of anamnesis and physical examination is consensual, the need for TTE and even for the electrocardiogram in population screening of athletes is not a matter of general agreement among cardiology associations.¹²⁰ However, if clinical evaluation suggests the likelihood of hypertrophic cardiomyopathy (or others of genetic origin), valvular heart disease or other structural cardiac changes, it becomes an essential investigative method (Table 9).

3. Heart Murmurs, Valvular Heart Disease, Valvar Prostheses and Endocarditis

3.1. Heart Murmurs

Heart murmurs are common findings, with prevalence between 5 and 52%.¹²¹ They are produced when the laminar blood flow becomes turbulent, such as in stenoses or valve refluxes, emitting sound waves that can be detected with the aid of the stethoscope. It is important that during physical examination, even in asymptomatic patients, careful auscultation is performed in order to define its characteristics.¹²² An innocent murmur can be defined as a short, smooth ejective noise (1 to 2+ in 4), audible at the left sternal border, followed by a second normal sound, in the absence of other abnormalities.¹²³ This finding, associated with normal chest x-ray and electrocardiogram, estimates a low probability of cardiac disease and, in this case, there is no need for complementary echocardiography.¹²⁴ However, due to inadequate training or maintenance of knowledge, characteristics of the murmur or patient's

anatomy, the auscultation may leave doubts about the existence of underlying organic causes. In such situations, the use of electronic stethoscope¹²⁵ and performing directed cardiac ultrasound,¹²⁶ if available, may be useful. In case of persisting doubt or suspicion of cardiac alteration, the echocardiography should be performed (Table 10). This systematic approach and investment in medical training allows for a rational use of resources, avoiding excessive diagnosis and unnecessary exams.¹²⁴

3.2. Native Valves

Echocardiography is the standard diagnostic method for assessing heart valves. TTE should be performed in suspected and in diagnosed valvular heart disease, for evolutionary follow-up of moderate and important lesions, and changes in clinical status.¹²⁴ The examination identifies the mechanisms involved, quantifies hemodynamic severity and repercussion, estimates prognosis, and assists treatment decision.^{127,128} In addition, physical exertion echocardiography can be performed to evaluate the behavior of echocardiographic parameters in asymptomatic patients and in cases of divergence between symptoms and the severity of the lesions estimated in the exams performed at rest.^{24,127,129} Besides traditional echocardiographic techniques, recent applications, such as the strain and the 3D, have provided new anatomical and functional information.¹³⁰⁻¹³²

3.2.1. Mitral Regurgitation

TTE, in addition to diagnostic confirmation, provides information necessary for follow-up and decision making in mitral regurgitation(MR).¹²⁷ TTE identifies dilation of

Table 9 – Recommendations of transthoracic echocardiography in the evaluation of athletes of competitive and/or professional physical activities

Recommendation	Class of recommendation	Level of evidence
In the differentiation of "athlete's heart" from conditions of pathological hypertrophy	I	B
Assessment for release of competitive physical activity, when clinical consultation demonstrates the possibility of hypertrophic cardiomyopathy or other genetically transmissible ones	I	B
Assessment for release of competitive physical activity, when clinical consultation shows signs of valvular heart disease or other structural cardiac changes	I	C
In routine assessment of athletes when there is no suggestion of ventricular overload or hypertrophy by clinical consultation or ECG	IIb	C

ECG: electrocardiogram.

Table 10 – Recommendations of transthoracic echocardiography in patients with murmur

Recommendation	Class of recommendation	Level of evidence
Asymptomatic patients, with murmur suggestive of cardiopathy	I	C
Asymptomatic patients with signs or exams (e.g., electrocardiogram) suggestive of cardiac disease	I	C
Patients with murmur and low probability of heart disease that cannot be ruled out by clinical investigation, electrocardiogram, chest X-ray or directed ultrasound	IIa	C
Patients without signs or symptoms suggestive of cardiopathy	III	C

Statement

cardiac cavities and dysfunction of both ventricles, in addition to allowing the classification of regurgitation into primary (due to valve lesions) or secondary (caused by changes in LV geometry). The 3D echocardiography is more accurate in volumetric measurements and left ventricular function; it can be useful in the evaluation of RV⁴ and allows better visualization of the valve apparatus and planning of interventions.^{12,133} The evaluation of the regurgitation degree can be made by the integrated approach of multiple qualitative and quantitative parameters: cavity dilations, pulmonary artery pressure, mitral inflow velocity, pulmonary vein flow pattern, mitral regurgitation density and duration analysis, calculus of the jet area or regurgitant volume, *vena contracta* measurement and regurgitant orifice measurement (flow convergence method, or proximal isovelocity surface area – PISA).¹³³ Challenging situations for echocardiography are the presence of multiple and/or eccentric jets, cardiac arrhythmias and acute MR. In these cases, special emphasis should be given to integrated analysis relating anatomical and hemodynamic parameters. The improvement of quantitative measures, such as PISA and *vena contracta*, through the 3D echocardiography, can aid in the evaluation of eccentric reflux.^{132,134} Another important point is the measurement of left ventricular function, especially in asymptomatic patients, which can be overestimated by LVEF measurement, with implications for deciding the best time for intervention and for postoperative outcomes. Recently, measurement of myocardial deformation (strain) has been studied to more sensitively identify ventricular dysfunction, but despite good prospects, it still requires more studies and standardization.^{131,135,136}

TEE, whether 2D or 3D, is indicated for evaluation of the regurgitation mechanism in the care of inappropriate transthoracic images or in discrepancies between echocardiographic and clinical parameters.^{4,133} The general

recommendations for the use of the various modalities of echocardiography in MR are contained in tables 11, 12 and 13.

3.2.2. Mitral Stenosis

The diagnosis of mitral stenosis (MS) using echocardiography makes it possible to define its probable etiology as a consequence of a wide evaluation of the valve anatomy.¹³⁷ The hemodynamic characterization of the gradients and valvular area, together with the description of thickening, leaflet mobility, subvalvar involvement and degree of calcification of the commissures, determines the progression stage of the disease and defines the most appropriate type of treatment when the disease is symptomatic. The joint interpretation of the echocardiography and the clinical symptoms determines the indication of surgical intervention or balloon catheter valvuloplasty.¹³⁷ Recently, MS has been grouped into four distinct categories, based on anatomy, Doppler evaluation, presence of pulmonary hypertension, repercussions on LA, and symptoms: stage A (patients at risk for MS); stages B and C (asymptomatic patients, but with hemodynamic changes); and stage D (symptomatic patients with hemodynamic changes). Table 14 describes the parameters that must be included in the echocardiography to make this evaluation complete.^{138,139} The use of TTE usually defines the anatomy and severity of the lesion (Table 15), but there are indications for the use of TEE, such as in situations of technically difficult echocardiographic window or 24 hours before balloon catheter valvuloplasty to rule out the presence of thrombi in the LA (Table 16).^{138,140,141} 3D echocardiography, in the TTE or TEE modalities, has been shown to allow better anatomical analysis and more accuracy in the valvar area calculated by planimetry.^{142,143} Physical or pharmacological stress echocardiography (dobutamine) may be used in the discordance between symptoms and resting echocardiography data.¹³⁸ Such phenomenon of incompatibility between symptoms and hemodynamic repercussion can result

Table 11 – Recommendations of transthoracic and stress echocardiography in mitral regurgitation

Recommendation	Class of recommendation	Level of evidence
Initial assessment of severity and MR mechanism	I	C
Periodic assessment of left ventricular dimensions and function in patients with moderate to severe MR without symptom changes	I	B
Patients with MR and modifications of signs or symptoms	I	B
Assessment in the first postoperative month	I	C
Assessment of hemodynamic changes and ventricular adaptation during pregnancy	I	C
Stress echocardiography in asymptomatic patients with severe MI to assess tolerance to physical efforts and hemodynamic changes	IIa	B
Stress echocardiography to assess discrepancy between severity of valve disease and symptoms	IIa	B
Stress echocardiography to evaluate left ventricular reserve	IIb	B
Assessment of ventricular mechanics (strain) for patients with borderline left ventricular function	IIb	B
3D TTE to assess preoperative anatomy and left ventricular function	IIb	C
Routine assessment of slight MR with LV normal function and dimensions	III	C

MR: mitral regurgitation; TTE: transthoracic echocardiography; LV: left ventricle.

Table 12 – Recommendations of transesophageal echocardiography in mitral regurgitation

Recommendation	Class of recommendation	Level of evidence
Intraoperative assessment to define the mechanism and to assist in valve repair	I	C
Unsatisfactory TTE for determination of severity and/or insufficiency mechanism, or for the assessment of LV function	I	B
Asymptomatic patients with severe MR to assess the possibility of valve repair	IIa	C
3D TEE to assess preoperative anatomy and left ventricular function	IIb	B
Assessment of patients with slight MR	III	C

TTE: transthoracic echocardiography; LV: left ventricle; MR: mitral regurgitation; TEE: transesophageal echocardiography.

Table 13 – Recommendations of echocardiography in patients with mitral valve prolapse

Recommendation	Class of recommendation	Level of evidence
Diagnosis, anatomical and functional evaluation of patients with physical signs of MVP	I	C
Confirmation of MVP in patients with previous diagnosis, but without clinical evidence to support it	I	C
Risk stratification in patients with clinic features or diagnosis of MVP	IIa	C
Exclusion of MVP in first-degree relatives of patients with myxomatous valve disease	IIb	C
Exclusion of MVP in patients with no suggestive physical signs or family history	III	C
Periodic echocardiographies in patients with MVP without insufficiency or with slight insufficiency, without alterations of symptoms or clinical signs	III	C

MVP: mitral valve prolapse.

from the disproportion between the valve area and the patient's body size, or the lack of complacency of the valve orifice (which should increase during exercise).¹⁴⁴ On a low-dose dobutamine echocardiography, the mean mitral transvalvular gradient should increase above 18 mmHg¹⁴⁵ in order for MS to be considered the cause of the symptoms, while on exercise echocardiography (treadmill), the significant cut-off value is one elevation above 15 mmHg.^{138,144} The increase in systolic pressure in the pulmonary artery is considered of clinical value only during the exercise echocardiography and should reach at least 60 mmHg so that pulmonary hypertension is considered secondary to MS. Other less frequent indications of a stress echocardiography may be found in asymptomatic patients with marked stenosis (Table 17).¹⁴⁴ Care should be taken to diagnose associated lesions in MS, whether it is a significant MI (which imposes a limitation on balloon catheter valvuloplasty) or lesions on other heart valves.

3.2.3. Aortic Stenosis

TTE is the first-line method (Table 18) for the diagnosis and assessment of the severity of aortic valve stenosis (AVS).^{128,146-148} The definition of the moment of surgical or percutaneous intervention depends on the integrated analysis of clinical and echocardiographic parameters (valvular anatomy, Doppler valvular hemodynamics and repercussion on cavity size and pulmonary artery pressure) that allow to classify aortic stenosis into four stages: stage A (risk of AVS); stage B (mild and moderate asymptomatic AVS); stage C (asymptomatic marked AVS), subdivided into C1 (with

Table 14 – Elements of echocardiographic evaluation of mitral stenosis

Parameter	Description
Valve anatomy	Presence of dome, commissural fusion
Doppler	PHT value
Two-dimensional or three-dimensional	Planimetry of the mitral valve area
Left atrium	Indexed volume
Pulmonary artery pressure	Assessment of tricuspid or pulmonary insufficiency

PHT: pressure half-time.

LVEF $\geq$ 50%) and C2 (LVEF < 50%); and stage D (classical symptomatic marked AVS).¹⁴⁹ In some AVS subgroups, valve area is reduced in the low gradient and low flow periods, either due to the concomitance of left ventricular dysfunction (LVEF < 50%) or the presence of small and hypertrophied LV, despite preserved LVEF). These subgroups are designated as stage D2 (with decreased LVEF) or D3 (with normal LVEF).^{146,147,150} In these discrepancy situations, in which valve area is $\leq$ 1.0 cm², the gradient is < 40 mmHg and LVEF is preserved (AVS with low paradoxical gradient or with low gradient and normal flow), additional methods such as TEE (3D, if possible), computed tomography or cardiac resonance may be necessary to confirm the severity of AVS.¹⁴⁷ TEE allows a better evaluation of the aortic valve anatomy

Statement

Table 15 – Recommendations of transthoracic echocardiography in mitral stenosis

Recommendation	Class of recommendation	Level of evidence
Establish diagnosis of patients with signs and symptoms of MS	I	B
Quantification of severity (PHT, gradients, valve area and pulmonary artery pressure)	I	B
Assessment of concomitant valve lesions	I	B
Determination of score for valvotomy by balloon catheter. Block Wilkins: thickening, mobility, subvalvar and calcification	I	B
Reassessment of stable MS with area < 1 cm ² each year	I	B
Reassessment of stable MS with area between 1 and 1.5 cm ² every 2 years		
Reassessment of stable MS with area > 1.5 cm ² in 3 to 5 years		
Immediate reassessment with change of symptoms		
Follow-up of balloon catheter valvuloplasty after dilatation	I	B
Assessment of hemodynamic alterations and adaptation during pregnancy	I	B

MS: mitral stenosis; PHT: pressure half-time.

Table 16 – Recommendations of transesophageal echocardiography in mitral stenosis

Recommendation	Class of recommendation	Level of evidence
Inconclusive transthoracic echocardiography	I	B
Assessment of thrombus preceding balloon catheter valvuloplasty	I	B
Assessment of the degree of mitral regurgitation preceding balloon catheter valvuloplasty (when there is doubt about transthoracic)	I	B

Table 17 – Recommendations of stress echocardiography in mitral stenosis

Recommendation	Class of recommendation	Level of evidence
Discordance between symptoms and valvar area/gradient (mitral area > 1.5 cm ²)	I	C
Assessment of asymptomatic patients with area < 1 cm ²	IIa	C
Assessment of asymptomatic patients with an area between 1 and 1.5 cm ² in pregnancy or major surgery planning	IIb	C

(valvular calcification), etiology (degenerative, congenital or rheumatic), LV exit path (diameter and geometry, mainly 3D) and greater accuracy in the calculation of valvular area, either by continuity equation or by direct planimetry.^{147,150} The absence of significant calcification should alert to the possibility of sub- or supra-valvar obstruction. In good-quality images, 3D TTE also allows for a more accurate LVEF assessment and a calculation of ejection volume (aortic transvalvular flow) by subtraction of final diastolic and systolic volumes, without the need to use LV exit pathway measurement and Doppler. This calculation, however, should be analyzed along with the other parameters, once it may also underestimate aortic transvalvular flow.^{147,150} If the calculation of the valve area is made during hypertension (blood pressure $\geq 140 \times 90$ mmHg), it should be repeated after blood pressure control because it may underestimate the transvalvular flow. Reduction in LV systolic function by GLS measurement, with no other explanation, in the presence of preserved LVEF, favors the diagnosis of severe AVS with

low paradoxical gradient. Stress echocardiography with low dose of dobutamine, with calculation of the projected area of the valve, if necessary,^{144,147} should be performed if there is marked aortic stenosis with low-flow/low gradient and left ventricular dysfunction (stage D2) to distinguish truly marked stenosis from pseudostenosis and to evaluate the contractile reserve (Table 19). Echocardiography under physical stress is recommended to unmask symptoms or to provide prognostic information on moderate or marked asymptomatic AVS with preserved LVEF (stages B or C) (Table 19). An increase in the mean pressure gradient (> 18 to 20 mmHg), the absence of contractile reserve and the increase of pulmonary artery systolic pressure (PASP) > 60 mmHg during exercise are parameters of worse prognosis and require follow-up at shorter intervals.¹⁴⁴ Stress echocardiography may also be useful in low-flow/low paradoxical gradient (with preserved LVEF), asymptomatic or with mild or doubtful symptoms, to confirm the severity of AVS using the same criteria.¹⁴⁴ In suboptimal images, the

evaluation of LVEF can be improved by the use of myocardial contrast, to better delineate endocardial borders.¹⁴⁷ The invasive hemodynamic study is restricted to situations in which noninvasive imaging tests are inconclusive.^{146,149} The follow-up interval with TTE depends on the stage of the disease and predictors of poor prognosis. Accentuated aortic valve calcification is another predictor of more severe stenosis and worse clinical progression.¹⁵¹ Marked AVS with low paradoxical gradient has worse prognosis when compared to classical AVS and the remaining AVS subgroups.¹⁵⁰ The paradoxical low gradient and normal flow ($LV > 35 \text{ mL/m}^2$) seems to have a prognosis similar to that of moderate AVS, but should be accompanied by shorter intervals, particularly if symptomatic.¹⁴⁷ In classical AVS, the maximum velocity $\geq 5 \text{ m/s}$ ¹⁵² and an annual increase in maximum velocity $\geq 0.3 \text{ cm/s}$ ¹⁵¹ in serial examinations (recorded in the same incidence and with the same quality) are predictors of worse prognosis and of faster progression.^{146,147,149}

In patients who are candidates for percutaneous implantation of aortic prosthesis for the treatment of AVS, 3D TEE can be used to evaluate the diameter of the ring, but it depends on the operator and image quality and should be used only when there is contraindication to computed tomography. On the other hand, 3D TEE is recommended to monitor the procedure and to evaluate outcomes or complications (Table 20).¹⁴⁸

3.2.4. Aortic Regurgitation

Echocardiography is the first-choice method to confirm diagnosis and etiology and to assess the severity and hemodynamic consequences of aortic regurgitation (AR).^{133,153} AR can be observed due to primary diseases of the aortic valve (AV) or to abnormalities of the aortic root and ascending aorta. Degeneration of AV and bicuspid aortic valve are the most common etiologies. Other causes include rheumatic fever, fibrosis or infection, alteration of the valvular apparatus support or dilatation of the valve ring. The integrated analysis of clinical and echocardiographic parameters (valve anatomy, aortic root and ascending aortic root diameters, Doppler valvular hemodynamics and repercussions on cavity size and pulmonary artery pressure) allows the classification of AR in four stages: stage A (risk of AR), stage B (mild to moderate asymptomatic AR), stage C [asymptomatic acute AR without (C1) or with dysfunction/dilation of LV (C2)]; and stage D (symptomatic acute AR).¹⁴⁹ In suboptimal images, LVEF measurement may be more accurate with the use of myocardial contrast to delineate the endocardial borders.¹³³ TEE (with 3D if available), tomography or cardiac resonance may be necessary to better assess the aortic root and ascending aorta (especially in the case of a bicuspid aortic valve), the severity of AR, or the quantification of LV ejection volumes and ejection fraction.¹³³ The appearance of symptoms in AR drastically changes prognosis. Effortless echocardiography may be indicated to reveal the presence of symptoms or to investigate other causes not related to AR (diastolic dysfunction, pulmonary hypertension or dynamic MI).¹⁴⁴ However, it should not be used to assess severity, once that increased heart rate shortens diastole, limiting quantification.¹⁴⁴ The follow-up interval with TTE depends on the stage of the disease and

the presence of aortic dilatation associated with bicuspid aortic valvopathy.^{148,154} Recommendations for the use of the various modalities of echocardiography in AR are set out in tables 21 to 24.

3.2.5. Tricuspid Valvulopathy

TTE is the first-line method for evaluating tricuspid valve abnormalities (Table 25).^{146,148,149} In most cases, tricuspid regurgitation (TR) is secondary to tricuspid ring dilatation and leaflet pull due to distortion and right ventricular remodeling, which occur due to volume or pressure overload caused by diseases of the left side of the heart, pulmonary hypertension, pulmonary valve stenosis, among others. In this context, leaflets are structurally normal. Primary causes of TR are rarer and may be due to infective endocarditis (mainly drug users), rheumatic heart disease, carcinoid syndrome, myxomatous disease, endomyocardial fibrosis, corneal rupture related to endomyocardial biopsy, Ebstein's anomaly, and congenital dysplasia, among others.¹³³ Similar to mitral and aortic valve disease, it can be classified into four stages (A to D).¹⁴⁹ A thorough analysis of valvular anatomy by TTE is fundamental for the diagnosis of the etiology and mechanisms involved. It is necessary to measure the diameter of the ring and the use of all indexes of RV systolic size and function.¹³³ These measures help in decision making regarding the moment of the surgery and in the surgical planning. In situations of doubt regarding the RV, 3D TTE can be used, although it still requires more validation. Cardiac resonance remains the gold standard.¹⁴⁶ In this context, TEE is not recommended due to the anterior location of the RV, which makes it difficult to see through the transesophageal route.¹⁴⁸ Significant primary TR requires intervention before RV impairment.^{146,149} Secondary TR is usually treated when left side valve disease is corrected. As in the other valvopathies, the echocardiographic follow-up interval depends on the stage of the disease, but the etiology of the disease must also be considered. In the case of secondary TR, it is appropriate to follow the recommendations described for left heart valve dysfunctions. Significant annular dilatation (≥ 40 or $> 21 \text{ mm/m}^2$) and dilatation or progressive RV dysfunction should alert for earlier follow-up.¹³³ Tricuspid stenosis (TS) is an uncommon condition that, if present, is frequently associated with TR of rheumatic origin.^{146,149} In this case, the presence of associated mitral stenosis is common, which is usually the predominant lesion. Other causes are rare, such as congenital diseases, drugs, Whipple's disease, endocarditis, and large right atrial tumor.¹⁴⁶ TS diagnosis is often neglected. Careful analysis of the subvalvular apparatus is essential to predict valve repair.¹⁴⁶ The integration of clinical and echocardiographic parameters related to TS (mean gradient > 5 to 10 mmHg , valve area $\leq 1.0 \text{ cm}^2$ and mean time of pressure drop $\geq 190 \text{ ms}$) classifies severity in stages C (marked asymptomatic) and D (marked symptomatic).¹⁴⁹

3.2.6. Pulmonary Valvulopathy

TTE is the initial recommended method to diagnose and evaluate the severity of pulmonary stenosis (PS) or regurgitation (PR), its etiology and effects on cardiac structure and right ventricular function (class I).^{133,149} In addition to assessing the valvular anatomy, investigation of the etiology requires a

Statement

Table 18 – Recommendations of transthoracic echocardiography in aortic valve stenosis

Recommendation	Class of recommendation	Level of evidence
Diagnosis and assessment of the severity of AVS in the presence of suspicious murmur or symptoms potentially related to AVS, such as: chest pain, dyspnea, palpitations, syncope, stroke or peripheral embolic event	I	B
Syncope	I	B
History of bicuspid AV in first degree relatives	I	B
Patients with AVS to assess wall thickness, LV size and function	I	B
Reassessment of patients with the AVS diagnosis with change of symptoms or signs	I	B
Suboptimum transthoracic contrast echocardiography (≥ 4 contiguous LV segments not seen), for assessment of LV function and calculation of the ejected volume	I	B
Annual reassessment of asymptomatic patients with marked AVS (maximal velocity ≥ 4 m/s) (stage C1), with reduction of the interval to 6 months if there are predictors of greater severity at rest (AV marked calcification, maximum velocity > 5.5 m/s, increase in maximal velocity ≥ 0.3 m/s/year and low-flow/low paradoxical gradient) or effort echocardiography*	I	B
Reassessment every 1 to 2 years of asymptomatic patients with moderate AVS (maximal velocity 3 to 3.9 m/s) (stage B), with reduction of the interval to 1 year if there are predictors of greater severity on echocardiography at rest or effort echocardiography*	I	B
Reassessment of asymptomatic patients with discrete AVS (maximal velocity 2 to 2.9 m/s) (stage B), every 3 to 5 years, with reduction for 1 year in the presence of marked calcification	I	B
Reassessment after hypertension control in patients with accentuated AVS with low-flow/low gradient and preserved LVEF	I	B
Monitoring of percutaneous implantation of aortic valve prostheses and results immediately after implantation (catheter, position, prosthesis function, regurgitation)	I	B
Assessment of complications immediately after percutaneous implantation of the aortic prosthesis (hypotension, coronary occlusion, LV dysfunction, LVOT obstruction, marked mitral insufficiency, prosthesis displacement, tamponade, right ventricular perforation, gas embolism, aortic dissection)	I	B
Early assessment (within 30 days) after percutaneous implantation of aortic prosthesis as to the degree of valve regurgitation (or paravalvarization) in the presence of suspected valve dysfunction	I	B
Reassessment in less than one year of changes in hemodynamic severity and LV function in patients diagnosed with moderate AVS, before or during pregnancy, or who will be submitted to situations of increased demand (non-cardiac surgery)	IIa	C
Good quality transthoracic 3D echocardiography for better assessment of valve morphology (especially in suspected bicuspid AV) and the degree of calcification	IIb	B
3D echocardiography in good-quality transthoracic image in symptomatic acute AVS with low gradient and preserved LVEF (D3), to reassess the diameter and geometry of the LVOT, to calculate the valvular area by planimetry or to calculate the valvular area by the continuity equation using the ejected volume measured directly by 3D (instead of the ejected volume derived from Doppler or two-dimensional Simpson)	IIb	B

AVS: aortic valve stenosis; AV: aortic valve; LV: left ventricle; LVEF: left ventricle ejection fraction; LVOT: left ventricular outflow tract; 3D: three-dimensional.

* Predictors of worse prognosis on resting echocardiography: marked aortic valve calcification and maximal velocity increase ≥ 0.3 m/s/year; on exercise echocardiography: increased mean pressure gradient (> 18 to 20 mmHg), absence of contractile reserve, and increased PASP (> 60 mmHg).

thorough evaluation of the RV, pulmonary ring, pulmonary artery trunk and its branches. Primary PS or PR (with leaflet involvement) are more often due to congenital diseases than acquired ones. Secondary PR occurs in situations of pulmonary hypertension. There is little literature on the quantification of the severity of PR on the echocardiography, but there is a consensus that it should be done in an integrated way with pulsed, continuous and color Doppler parameters; and graded as mild, moderate, or marked.¹³³ PS and PR are classified, from the clinical-echocardiographic point of view, as stage C (marked asymptomatic) and D (marked symptomatic).¹⁴⁹ Evaluation of the pulmonary valve may be difficult for TTE. In this situation, however, the TEE does not provide additional information and is not recommended (class III). There is little

data on the value of 3D echocardiography. In cases of limited transthoracic imaging or severity parameters inconclusive or discordant with clinical data, cardiac resonance is recommended as the best method.¹³³

3.2.7. Associated Valvar Lesions

Associated valvular lesions (AVL) in our setting are frequent due to the high prevalence of rheumatic fever (RF), which reaches 70% of valvular heart disease in Brazil.¹⁴¹ In the EuroHeart Survey, 51% of AVL patients had RF and 40% had degenerative valve disease.¹⁵⁵ Pathophysiology is complex, because it depends on the specific combination of each valve lesion, and its diagnosis is challenging because the guidelines

Table 19 – Recommendations of stress echocardiography in aortic valve stenosis

Recommendation	Class of recommendation	Level of evidence
Low-dose dobutamine stress echocardiography to confirm symptomatic low-flow/low gradient AVS and reduced LVEF and to assess the presence of contractile reserve (stage D2)	I	B
Stress echocardiography in asymptomatic patients with moderate or marked AVS (stages B and C1) to assess exercise-induced symptoms, abnormal responses to systemic or pulmonary arterial pressure, and behavior of gradients and left ventricular function	IIa	B
Stress echocardiography in asymptomatic patients (or with mild or doubtful symptoms) with low-flow/low gradient AVS and preserved LVEF to differentiate true stenosis from aortic pseudostenosis	IIb	B
Stress or dobutamine echocardiography in symptomatic marked AVS	III	C

AVS: aortic valve stenosis; LVEF: left ventricle ejection fraction.

Table 20 – Recommendations of transesophageal echocardiography in aortic valve stenosis*

Recommendation	Class of recommendation	Level of evidence
High acuity AVS with low-flow/low gradient and preserved LVEF (D3), for assessment of valve area (reassessment of LVOT measurement) and assessment of valve morphology, including degree of calcification	I	B
Acute AVS with low flow/low gradient and reduced LVEF (D2) for assessment of valve morphology, including degree of calcification	IIb	B
Disagreement between the severity of AVS and transthoracic examination and clinical evaluation	I	B
Difficulty assessing AVS at transthoracic examination due to inadequate acoustic window	I	B
Assessment of aortic valve annulus size and geometry in patients candidates for percutaneous aortic valve prosthesis implantation	I	B
Monitoring of percutaneous implantation of aortic valve prostheses and results immediately after implantation (catheter, position, prosthesis function, regurgitation)	I	B
Assessment of complications immediately after percutaneous implantation of the aortic prosthesis (hypotension, coronary occlusion, LV dysfunction, LVOT obstruction, marked mitral insufficiency, prosthesis displacement, tamponade, right ventricular perforation, gas embolism, aortic dissection)	I	B
Early assessment (within 30 days) after percutaneous implantation of aortic prosthesis as to the degree of valvular or paravalvular regurgitation) in the presence of suspected valve dysfunction	I	B
Stroke after percutaneous implantation of aortic prosthesis in case of suspected valve dysfunction	I	B
Assessment of the distance of the aortic valve annulus to the coronary sinus in patients candidates for percutaneous implantation of aortic valve prosthesis	IIb	B

*3D, if available. AVS: aortic valve stenosis; LVEF: left ventricular ejection fraction; LVOT: left ventricular outflow tract; LV: left ventricle.

Table 21 – Recommendations of transthoracic echocardiography in aortic regurgitation¹⁵³

Recommendation	Class of recommendation	Level of evidence
Confirm the presence, etiology, and severity of acute or chronic AR	I	B
In patients with dilation of the aortic root to assess the degree of AR and the magnitude of aortic dilatation	I	B
Reassessment of patients with prior AR and change of symptoms or signs	I	B
Annual reassessment of LV size and function in marked asymptomatic AR, with reduction of the interval to six months for the first examination, or if there are significant changes in diameters or LVEF on subsequent examination (stage C)	I	B
Reassessment every one to two years in moderate asymptomatic AR (stage B)	I	C
Reassessment every three to five years in asymptomatic mild AR (stage B)	I	C
Reassessment in less than one year of hemodynamic severity and LV function in patients diagnosed with AR before or during pregnancy, or who will undergo situations that increase demand (non-cardiac surgery)	IIa	C

AR: aortic regurgitation; LV: left ventricle; LVEF: left ventricle ejection fraction.

Statement

Table 22 – Recommendations of transthoracic echocardiography in patients with bicuspid aortic valve and ascending aorta dilatation

Recommendation	Class of recommendation	Level of evidence
Assessment of aortic root and ascending aorta diameter in patients with bicuspid aortic valve	I	B
Annual reassessment of size and morphology of the aortic root and ascending aorta in a patient with a bicuspid aortic valve and aortic diameter between 4.0 and 4.5 cm, if the size remained stable within the first 6-month interval after the first exam	I	B
Six-monthly reassessment of the aortic root and ascending aorta size and morphology in a patient with a bicuspid aortic valve and one of the following criteria: aortic diameter > 4.5 cm; rapid increase in aortic diameter (> 0.3 cm); family history of aortic disease in a first degree relative; or if it is the first examination to detect aortic dilatation	I	B

Table 23 – Recommendations of stress echocardiography in aortic regurgitation¹⁵³

Recommendation	Class of recommendation	Level of evidence
Stress echocardiography in asymptomatic or marked AR with doubtful symptoms to evaluate exercise-induced symptoms and functional capacity	IIa	B
Stress echocardiography in moderate AR with evident or doubtful symptoms to confirm and exclude other causes	IIa	B
Echocardiography under stress with exercise or with dobutamine when there is a discrepancy between the severity of AR to the transthoracic echocardiography and clinical symptoms, to better quantify the AR	III	C

AR: aortic regurgitation.

Table 24 – Recommendations of transesophageal echocardiography in aortic regurgitation*¹⁵³

Recommendation	Class of recommendation	Level of evidence
Discrepancy between qualitative and quantitative parameters of transthoracic echocardiography and/or between echocardiography and clinical evaluation regarding the severity of AR	I	B
Confirm the presence, etiology and severity of acute AR if the transthoracic echocardiography is of limited, doubtful or inconclusive quality	I	B
In patients with a bicuspid aortic valve to assess the diameter of the aortic root and ascending aorta when the transthoracic image is suboptimal	I	B

*3D, if available. AR: aortic regurgitation.

Table 25 – Recommendations of the echocardiography in tricuspid valvulopathy

Recommendation	Class of recommendation	Level of evidence
2D TTE is recommended to confirm diagnosis, to assist in identifying the etiology and mechanisms of tricuspid lesions, to determine severity, to assess pulmonary pressure, as well as the dimensions of the cardiac cavities and the right ventricle function and to characterize any associated cardiac disease on the left side	I	B
TEE (with 3D if available) may be used for more detailed assessment of valve morphology, mechanisms and Doppler quantification if the TTE is of limited, doubtful or inconclusive quality, or there is a discrepancy between the clinical data and the echocardiographic findings	I	B
3D TTE (in optimal windows) can be used to assess systolic and diastolic volumes and RV systolic function in patients with marked TR (stages C and D)	IIb	B
TEE (2D or 3D) for assessing the systolic function of the RV in marked TR	III	C

TTE: transthoracic echocardiography; 2D: two dimensional; TEE: transesophageal echocardiography; 3D: three dimensional; RV: right ventricle; TR: tricuspid regurgitation.

provide us with specific valvular parameters alone. AVL may result from two primary valvular diseases¹⁵⁶ or from the combination of primary and secondary valvular disease.¹⁵⁷ Despite the high prevalence of AVL, there is little evidence of the best course of action to be taken in each combination. The most common combinations and their most frequent changes are reported below:¹⁵⁶

- AS and MI: Increased LV pressure caused by aortic stenosis may increase the regurgitant orifice and decrease aortic transvalvular gradients, mimicking a low-flow state.^{156,158} In some AS cases, there may be MR secondary to dilation and left ventricular dysfunction (tethering). Less frequent, but possible in these patients, is the presence of primary MR.

- AS and MS: are cases of difficult clinical control, in which the patient rapidly evolves to low throughput states. The gradients of both valves may be underestimated, and if the patient is inadvertently submitted to balloon catheter valvotomy of the mitral valve, acute pulmonary edema may occur due to the lack of LV compliance as a consequence of AS.^{141,156}

- AR and MS: the presence of MS limits the increase in ventricular volumes frequently observed in AR; which may underestimate the severity of AR.^{141,156}

- MR and AR: as a consequence of the volume overload imposed by both valvopathies, these patients usually have earlier contractile deficit than with each isolated valvopathy and progress more rapidly to the symptomatic phase of the disease.^{141,156,158}

Recommendations for TTE and TEE in AVL are listed in tables 26 and 27, respectively. The frequency at which TTE should be performed is debatable and depends on the type of AVL and symptomatology; in general, the examination should be repeated according to the predominant valve lesion guideline.¹⁵⁶ In the case of balanced lesions, TTE should be repeated with a shorter interval than the one suggested for a single valve lesion.¹⁵⁶

3.3. Valvular Prostheses

TTE is recommended as a first line examination for the analysis of valvular prostheses. TEE may be necessary when it is necessary to better evaluate the structure and complications of valvular prostheses, recommended in cases of dysfunction (Table 28). When performing the echocardiographic examination of valvular prostheses, it is necessary to know and document the reason for the investigation, the patient's symptomatology, the type and size of the prosthesis, the date of surgery, blood pressure, heart rate, height, weight and the patient's body surface area.²⁴ A detailed postoperative TTE is recommended four to six weeks after surgery, when the thoracic surgical incision is healed, thoracic wall edema resolved, and left ventricular function recovered. In this examination, it is important to record: cavity dimensions, ventricular function, prosthetic gradients, valvular areas, presence of functional or pathological refluxes, pulmonary pressure and alterations of other valves; defining the basal conditions of valve prostheses, since the examination will be taken as reference for serial assessments. Regarding the periodicity of TTE in patients with prosthesis, a frequent assessment in asymptomatic patients with supposedly normal mechanical prosthesis is not recommended. For biologic prostheses considered to be normal, exams after five (ESC)¹⁵⁹ or ten years (ACC/AHA) are recommended.¹²⁷ However, annual examinations are recommended in patients with new design prostheses that have not had their proven durability in patients with aortic dilatation at the time of surgery and in patients with mitral prostheses to evaluate the evolution of tricuspid regurgitation and RV function. Echocardiographic investigation (TTE and TEE) is recommended when changes in cardiac auscultation, onset of symptoms or suspicion of prosthesis dysfunction occur. In cases where there is clinical suspicion of infective endocarditis or thrombosis, the analysis should be more thorough.¹²³ In cases of significant reflux of prostheses, it is recommended to perform evolutionary TTEs every three to six months.¹²⁸ TEE, due to its proximity and

Table 26 – Recommendations of transthoracic echocardiography in associated valve lesions

Recommendation	Class of recommendation	Level of evidence
Establish diagnosis of patients with multiple murmurs	I	C
Quantification of the severity of stenoses and associated insufficiencies	I	C
Immediate reassessment with change of symptoms	I	C
Annual reassessment of asymptomatic patients with AVL	IIa	C

AVL: associated valvular lesions.

Table 27 – Recommendations of transesophageal echocardiography in associated valve lesions

Recommendation	Class of recommendation	Level of evidence
Inconclusive transthoracic echocardiography	I	C
Doubts in the quantification of valvular lesions	I	C
Monitoring of invasive procedures for injuries that can be treated percutaneously	I	C

Statement

posterior approach to the heart, achieves better diagnostic precision in valvular prosthesis dysfunctions. In fact, TTE and TEE complement each other, since the TTE better evaluates the changes in flow and TEE, the morphological changes. It is always advisable to carry out the full and careful TTE before recommending the TEE. The 3D TEE¹⁶⁰ provides additional information about the 2D image, particularly regarding the spatial relationship of the structures around the prosthesis, the direction and extent of regurgitant jets, the location of paravalvular leaking and the identification, position and number of larger anomalous prosthetic or periprosthetic echoes, potentially more embolinogenic.¹⁶¹ The diagnosis of prosthesis stenosis should always be performed with the extensive use of echocardiography. The transprosthetic gradients are variable in each model and size, and there may be high gradients in cases of small, even normal, prostheses when implanted in large body surface patients, a finding known as mismatch.¹⁶² Patients who remain with significant LVH in the late postoperative period may also present elevated gradients after aortic prosthesis implantation. Thus, the comparison with the basal echocardiography is always important. In biological prostheses, the most frequent cause of stenosis is the degeneration and calcification of the leaflets, usually a late complication. In mechanical prostheses, the growth of fibrous tissue into the ring, known as pannus, is also a late complication that can cause stenosis, reflux, or double prosthetic dysfunction. The detection and quantification of the reflux of the prostheses are usually

hampered by the acoustic shadow caused by the mechanical prostheses, mainly in the mitral position. In such cases, TEE can aid in the detection and quantification, and determine if the insufficiency is prosthetic or periprosthetic, functional or pathological. We must be careful in differentiating the “physiological” refluxes, which are common in prostheses, from the pathological ones.¹⁶³ In general, physiological reflux presents laminar flow at color Doppler and pathological reflux presents a turbulent, color mosaic flow. In cases of suspicion of infective endocarditis in prosthetics, the diagnosis is made difficult by the presence of shadows and reverberations, allowing the TTE to identify only the large vegetation. Given the clinical suspicion of endocarditis, it is always advisable to perform the TEE, which has greater sensitivity, detecting smaller vegetations and possible complications, such as annular abscesses (Table 29). 3D TEE allows a more precise spatial localization, in relation to the adjacent prosthetic and anatomical structures, of potentially emboligenic vegetations. In cases of embolic phenomena or acute stenosis of the prosthesis, especially in the mitral position, the presence of valve thrombosis or strands (fibrin) should be suspected, with TTE and TEE being indicated (3D TEE, if possible) in order to overcome the acoustic shadow and better observe the LA and the atrial face of the prosthesis. In these cases, in addition to looking for thrombi or fibrin in the valve or the LA, the prosthesis’ mobile structures and the emboligenic potential of the thrombi should be functionally evaluated (Table 30).

Table 28 – Recommendations of echocardiography in valvular prostheses

Recommendation	Class of recommendation	Level of evidence
TTE in patients with valve prostheses with changes in clinical signs or symptoms, suggesting prosthetic dysfunction (stenosis or insufficiency)	I	A
TEE in patients with prosthetic dysfunction to TTE, for confirmation and better quantification of dysfunction	IIa	B
Periodic reassessment in patients with prosthesis, with ventricular dysfunction without modification of symptoms or clinical signs	IIa	B
Periodic reassessment in biological valve prostheses without signs or symptoms of prosthetic dysfunction	IIb	B

TTE: transthoracic echocardiography; TEE: transesophageal echocardiography.

Table 29 – Recommendations of echocardiography in infective endocarditis in patients with valve prostheses

Recommendation	Class of recommendation	Level of evidence
Detection and characterization of the valve lesion and evaluation of the hemodynamic repercussion*	I	B
Detection of complications such as abscesses, ruptures and fistulas*	I	B
Reevaluation in cases with poor clinical evolution*	I	B
Suspected endocarditis in patient with negative cultures*	I	B
Bacteremia of unknown etiology*	I	B
Persistent fever with no evidence of bacteremia or new murmurs*	IIa	B
Routine assessment during treatment of uncomplicated endocarditis*	IIb	B
Transient fever without evidence of bacteremia or new murmur*	III	B

** Transesophageal echocardiography may give additional information to those obtained with transthoracic echocardiography.*

Table 30 – Recommendations of echocardiography in patients with clinical suspicion of valvular prosthesis thrombosis

Recommendation	Class of recommendation	Level of evidence
Carrier of mechanical prosthesis with embolic phenomenon and/or acute heart failure	I	B
Assessment to determine the hemodynamic changes caused by thrombosis	IIb	B
TEE to complement the TTE, to evaluate the mobility and emboligenic potential of the thrombi and functional study of the prosthesis	IIb	B

TEE: transesophageal echocardiography; TTE: transthoracic echocardiography.

3.4. Infective Endocarditis

Infective endocarditis (IE) is vascular or cardiac endocardial infection resulting from invasion of microorganisms. Despite the advances in diagnostic techniques and treatment, mortality by IE remains high.¹⁶⁴ The profile of the disease presentation changed, with the emergence of new risk groups and more virulent microorganisms, with staphylococci emerging as the main etiological agents. Echocardiography is fundamental in the IE approach (Table 31).¹⁶⁵⁻¹⁶⁸ The best resolution of the devices and, especially, the use of TEE are responsible for the high accuracy of the method in the diagnosis and evaluation of complications. The additional value of TEE when TTE is not diagnostic is well defined in the strong clinical suspicion of IE and/or the presence of valvular prostheses. However, the indication of TEE as an initial examination needs to be validated by new studies.¹⁶⁸ The definitive diagnosis of IE is based on positive blood cultures and/or characteristic echocardiographic findings. The findings following the echocardiography are major diagnosis criteria: vegetation defined by a mobile condensed mass, adhered to the valvar endocardium, mural or implanted prosthetic material; abscesses or fistulas; new prosthesis dehiscence (especially when it occurs late after its implantation) and new valve regurgitation.¹⁶⁹

4. Hypertension and Pulmonary Thromboembolism

Pulmonary hypertension (PH) is a clinical condition associated with high morbidity and mortality, the prevalence of which is unknown due to different presentation groups. From the knowledge of the various pathophysiological mechanisms, the current classification divides PH into five groups.¹⁷⁰ Regardless of the mechanism, it is defined as mean pulmonary arterial pressure greater than or equal to 25 mmHg, at rest, documented by cardiac catheterization.¹⁷⁰ Currently, TTE is considered a method of fundamental importance in the initial evaluation of patients with clinical suspicion of PH (Table 32), since it offers information related to: diagnosis, hemodynamic status, therapeutic response and prognosis.¹⁷¹ Hemodynamic data, such as pulmonary artery systolic pressure, mean arterial pressure, pulmonary artery occlusion pressure and blood volume (assessed by varying the size of the inferior vena cava), can be measured by this method.¹⁷² The presence of RV hypertrophy, enlargement of the right cavities, anomalous movement of the septum and pericardial effusion suggest the diagnosis. The analysis of the contractile function of the RV is performed through the TAPSE, s-wave (systolic) of the tissue Doppler, RV area fractional variation and ejection fraction

Table 31 – Recommendations of transthoracic echocardiography and transesophageal echocardiography in infectious endocarditis

Recommendation	Class of recommendation	Level of evidence
TTE is indicated as the first examination in the clinical suspicion of IE	I	B
TEE is indicated on clinical suspicion of IE and negative or non-diagnostic TTE	I	B
TEE indicated in the diagnostic suspicion of IE in patients with valvular prostheses and intracardiac devices	I	B
Indicated to repeat TTE or TEE within five to seven days in the face of high clinical suspicion and initial negative TEE	I	C
Echocardiography indicated for the assessment of staphylococcal bacteremia of unknown source	IIa	B
TEE may be indicated for suspected IE, even in cases with positive TTE with good quality and reliable findings (except isolated IE)	IIa	C
New TTE or TEE indicated for suspected new complications (abscesses, perforations, embolisms, persistence of fever, heart failure)	I	B
New TTE or TEE indicated for the follow-up of uncomplicated IE, for vegetation size monitoring or detection of silent complications. The type (TEE or TTE) and the date of the new examination will depend on the initial findings, type of microorganism and response to therapy	IIa	B
Intraoperative TEE in all cases of valve surgery by IE	I	B
At the end of the treatment to establish new parameters of cardiac and valvular morphology and function	I	C

TTE: transthoracic echocardiography; IE: infective endocarditis; TEE: transesophageal echocardiography.

Statement

to the 3D.⁴ Right cardiac catheterization remains the gold standard for diagnosis, since it allows the direct measurement of hemodynamic data in the pulmonary circulation and evaluates the capacity of response to vasodilator therapy through the pulmonary vasoreactivity test.

Pulmonary thromboembolism (PTE) is another clinical condition of high mortality, which can cause complications such as chronic thromboembolic pulmonary hypertension (PH group IV).¹⁷⁰ Clinical suspicion, progress in diagnosis, and effective therapy are critical in reducing mortality in the acute event. The sensitivity and specificity of TTE for the diagnosis of PTE are 50 to 60% and 80 to 90%, respectively. In critical patients, TEE may increase this sensitivity. The visualization of the thrombus in the right atrium (RA), in the RV or in the trunk of the pulmonary artery ratifies the diagnosis. However, indirect signs are more commonly found, such as dilatation of the right cavities, RV contractile dysfunction, interventricular septal flattening, McConnell's signal (apical region with preserved contractility and akinetic mean free wall segment, with sensitivity of 77% and specificity of 94%) and dilation of the inferior vena cava. The pulmonary artery acceleration time is a parameter with good sensitivity, since it is altered (< 100 ms) in cases of small pulmonary embolism.¹⁷³ RV strain is an important tool because it shows the segment that presents reduced value and evaluates its deformity after reperfusion therapy. Patients who develop contractile dysfunction of the RV or patent foramen ovale present a reserved prognosis.

5. Coronary Artery Disease

5.1. Introduction

Coronary artery disease has a wide clinical spectrum, ranging from asymptomatic severe disease,¹⁷⁵ long-term stable angina or acute coronary syndrome (ACS)/acute myocardial infarction (AMI) with hemodynamic instability as the first manifestation of the disease.^{176,177} The echocardiography has

applications in its diagnostic recognition, stratification of risk in the acute phase, follow-up and determination prognosis in the long term.^{178,179}

5.2. Acute Coronary Syndrome

5.2.1. Transthoracic Echocardiography

In the scenario of a patient with acute chest pain and suspected coronary artery disease, echocardiography may be useful (Table 33) and should be routinely available in the emergency department and thoracic pain units.¹⁸⁰ Evidence of new or presumably contractile change from LV to TTE is one of the parameters in the third universal definition of myocardial infarction¹⁸¹ and may in fact assist in the diagnosis/prognostic determination of an ACS. In addition, TTE may aid in the differential diagnosis of chest pain and/or associated conditions, such as acute aortic dissection, aortic stenosis, hypertrophic cardiomyopathy, and pulmonary embolism.¹⁸⁰ By dividing LV into 16 or 17 segments, contractile segmental function is visually quantified based on systolic thickening (ST): hyperkinetic = 0 (ST > 70%); normal = 1 (ST = 50 to 70%); hypokinetic = 2 (ST < 40%); akinetic = 3 (ST < 10%); "dyskinetic" = 4 (paradoxical movement/systolic expansion)". The wall motion score index (WMSI) is the reference parameter to express the LV segmental function and its normality value is 1; values between 1 and 1.6 show a contractile alteration of mild degree; while WMSI values above 1.6 indicate greater involvement and worse prognosis.¹⁸² Obviously, the absence of alterations in segmental contractility in resting TTE does not exclude the presence of coronary artery disease.¹⁸⁰ It should also be considered that the contractile alteration may occur in other conditions such as myocarditis, RV overload (volume/pressure), ventricular pre-excitation, Takotsubo type cardiomyopathy, left bundle branch block, chagasic cardiomyopathy or presence of pacemaker.¹⁸⁰ TTE is the exam of choice in cases of hemodynamic instability with suspected cardiac origin, as well as in the identification of mechanical complications of AMI.^{179,180} However, it is necessary to avoid

Table 32 – Recommendations of the echocardiography in pulmonary hypertension and thromboembolism^{170,174}

Recommendation	Class of recommendation	Level of evidence
TTE recommended as a first line examination for noninvasive diagnostic investigation of suspected pulmonary hypertension	I	C
TTE recommended in the assessment of signs of pulmonary hypertension in symptomatic patients with portal hypertension or liver disease and in all indicated to hepatic transplantation	I	B
TTE recommended as an initial examination for the assessment of pulmonary hypertension in patients with systemic sclerosis and annually	I	C
TTE recommended for noninvasive diagnostic assessment of patients with pulmonary disease with suspected pulmonary hypertension	I	C
High-risk pulmonary embolism, in the presence of shock or hypotension, TTE at the bedside or angiotomography (depending on the patient's clinical conditions or availability)	I	C
High-risk pulmonary embolism with signs of right ventricular dysfunction, unstable for angiography (TTE at the bedside with Doppler of lower limbs and/or TEE to assess pulmonary artery thrombus)	IIb	C
Not recommended in asymptomatic HIV positive patients for the detection of pulmonary hypertension	III	C

TTE: transthoracic echocardiography; TEE: transesophageal echocardiography; HIV: human immunodeficiency virus.

requesting the examination for evaluation of patients with chest pain with a confirmed diagnosis of myocardial ischemia (ACS/AMI), since TTE should not delay the immediate onset of treatment.^{176,177,180} On the other hand, in the screening of symptomatic patients suspected of having coronary artery disease in the emergency room, recent evidence indicates the potential usefulness of GLS calculated by 2D speckle tracking. In the absence of preexisting structural heart disease, previous infarction or left bundle branch block, GLS (when $< 16.5\%$) may complement existing diagnostic algorithms and act as an early adjunct marker of ischemia.¹⁸³

5.2.2. Stress Echocardiography

The evidence of a new alteration of the segmental contractility at rest or its appearance before the induction of stress (exercise or pharmacological) suggests ischemic etiology.¹⁸⁴ Stress echocardiography is an independent

predictor of cardiovascular death, of additional value to the other methods and can avoid coronary angiography.^{175,179} Its use may be recommended for risk stratification of patients in chest pain units (Table 34), especially when the electrocardiogram does not define the diagnosis and the exercise test is submaximal, non-feasible or inconclusive.¹⁷⁹ Traditionally, stress echocardiography is performed after 24 hours of chest pain relief in low to moderate risk patients with no evident ischemic changes on the electrocardiogram and normal cardiac enzymes.

5.2.3. Contrast Echocardiography

This echocardiographic modality allows the immediate and simultaneous access of LV segmental contraction and myocardial perfusion.^{179,180} In patients with acute chest pain and non-diagnostic electrocardiogram, the use of contrast echocardiography increases sensitivity for the diagnosis of

Table 33 – Recommendations of transthoracic echocardiography in acute coronary syndrome

Recommendation	Class of recommendation	Level of evidence
Assessment of global and segmental ventricular function	I	C
Differential diagnosis of alternative causes of chest pain: severe aortic stenosis, hypertrophic cardiomyopathy, pulmonary embolism, aortic dissection*, pericarditis and the presence of cardiac tumors	I	C
Chest pain with hemodynamic instability and suspected cardiac origin	I	C
Suspected mechanical complications in myocardial infarction: left ventricular aneurysm, rupture of free wall or papillary muscle, ventricular septal defect, pericardial effusion	I	C
Assessment of right ventricular impairment in the presence of inferior wall myocardial infarction	I	B
During chest pain of possible ischemic origin, with electrocardiogram and non-conclusive cardiac enzymes	IIa	B
Calculation of global longitudinal strain using speckle tracking as an adjunct to existing diagnostic algorithms and risk classification in patients with suspected coronary disease&	IIa	B
Assessment of patients in the presence of chest pain with a confirmed diagnosis of myocardial ischemia/infarction	III	C
Evaluation of chest pain in patients whose non-cardiac etiology is evident	III	C

* Complementation with transesophageal echocardiography increases accuracy and can provide additional information to the transthoracic one; &in the absence of preexisting structural heart disease, prior myocardial infarction, or left bundle branch block.

Table 34 – Recommendations of stress echocardiography in acute coronary syndrome

Recommendation	Class of recommendation	Level of evidence
Patients with clinically controlled low risk unstable angina* before deciding the invasive strategy	IIa	A
To assess the functional significance of moderate coronary obstruction at angiography, as long as the result interferes with the procedure	IIa	C
Risk stratification after uncomplicated myocardial infarction	IIa	A
Investigation of patients with suspected microvascular disease& to establish whether segmental change occurs in conjunction with angina and electrocardiographic abnormalities	IIa	C
Strain and strain rate parameters derived from speckle tracking as an adjunct tool to wall motion score index for diagnosis and/or prognosis of acute coronary disease	IIa	B
High risk unstable angina or acute myocardial infarction	III	C

* No recurrence of angina, no signs of heart failure, no abnormalities on the initial/serial electrocardiogram and normal troponin; &typical angina pain with electrocardiogram change or functional test, in the presence of normal coronary angiography.

Statement

ACS (Table 35).180,185 Patients with normal perfusion and myocardial function at rest have good prognosis, while the presence of perfusion defects at rest identifies a subgroup at high risk for ACS.¹⁸⁵

5.3. Chronic Coronary Artery Disease

5.3.1. Transthoracic Echocardiography

TTE, while providing important information on segmental contractility when performed at the time of acute chest pain, is limited in the investigation of patients with chronic coronary disease.¹⁷⁵ Two situations of indication should be valued: the first one when there is a need for a differential diagnosis of chest pain with non-ischemic causes, such as pericarditis, valvular diseases (such as aortic stenosis) or cardiomyopathies that may occur with chest pain; the second is based on the knowledge of global left ventricular function as a prognostic factor in stable patients with chronic coronary disease (Table 36).¹⁷⁵

5.3.2. Stress Echocardiography

Stress echocardiography is a useful investigative method for both suspected patients and those with an established diagnosis of stable coronary disease (Table 37). The method offers good accuracy in the ischemic investigation of patients from moderate to high risk, with a slight predominance of specificity compared to other non-invasive imaging methods, such as myocardial scintigraphy.^{179,184,186,187} The stress-induced modality, whether physical, with treadmill or bicycle, or pharmacological, with dobutamine sensitized with atropine or even with dipyridamole, does not significantly change the diagnostic performance of the test.¹⁷⁹ In general,

in the investigation of stable coronary disease, stress echocardiography should be indicated for those patients with limited exercise performance, either by functional class or by non-interpretable electrocardiogram, such as in the presence of left bundle branch block.¹⁸⁸ Thus, the method should not be considered as a substitute for the ergometric test. However, if available, it can be used as the first examination in the investigation of selected patients, with intermediate or high pretest probability. Furthermore, in the investigation of the risk of chronic coronary disease, it can be used as a sequential method to others such as coronary tomography, when the calcium score shows levels above 400.^{184,186} Another important clinical situation for indication of stress echocardiography is the preoperative evaluation of patients undergoing intermediate-risk surgery.^{179,187,189} Even in this situation, the method can be used but it should not generally replace the exercise test when this is possible. However, in vascular surgeries, where there are one or more risk factors, the investigation may start from the echocardiographic examination under stress.¹⁸⁴ Situations in which there is a need for the topographical definition of ischemia, such as those of a functional significance investigation of already known lesions, also induce the image examination under stress, which may be the echocardiography. However, the availability of the method in the region of medical practice and the technical ability and experience of the echocardiography laboratory for individualized application of the levels of recommendation suggested here should be considered.

5.3.3. Contrast Echocardiography

The use of echocardiographic contrast agents consisting of microbubbles capable of overcoming the pulmonary barrier and remaining intact has become a powerful

Table 35 – Recommendations of contrast echocardiography in acute coronary syndrome

Recommendation	Class of recommendation	Level of evidence
Use of echocardiographic contrast for better definition of the endocardial border and to access left ventricular structure/function when two or more adjacent segments are not visible in the standard resting or stress tests	I	B
Assessment of patients with acute chest pain and non-diagnostic electrocardiogram	IIb	B
Assessment of myocardial perfusion in all types of ACS	III	C
Routine use of echocardiographic contrast in all patients with chest pain and suspected CAD	III	C

ACS: acute coronary syndrome; CAD: coronary artery disease.

Table 36 – Recommendations of transthoracic echocardiography in chronic coronary disease

Recommendation	Class of recommendation	Level of evidence
Differential diagnosis of precordial pain	I	B
Initial assessment of left ventricular function as a prognostic indicator, even in patients with no evidence of heart failure	I	B
Assessment of left ventricular function when there is evidence of heart failure or change in clinical status	I	B
Periodic reassessment of stable patients without clinical change	III	C

Table 37 – Recommendations of stress echocardiography in patients with known or suspected chronic coronary disease

Recommendation	Class of recommendation	Level of evidence
As an initial method in the investigation of chronic coronary disease in patients with intermediate or high pre-test probability	I	B
As an initial method in the investigation of chronic coronary disease in patients with low pretest probability, but unable to perform an exercise test or with electrocardiogram not interpretable	I	B
As a sequential method in the investigation of patients submitted to an ergometric test with intermediate or non-diagnostic result	I	B
As a sequential method in the investigation of patients submitted to coronary tomography with a calcium score (Agatston) > 400	I	B
As a sequential method in the investigation of patients submitted to coronary angiography with identified lesions of uncertain functional significance	I	B
In the preoperative evaluation of non-cardiac vascular surgery in a patient with one or more risk factors for chronic coronary disease	I	B
In the assessment of viability in patients with ventricular dysfunction and chronic coronary disease and eligible for revascularization	I	B
In the preoperative assessment of non-cardiac intermediate risk surgery in a patient with one or more risk factors for chronic coronary disease with functional class < 4 METs or indeterminate	IIa	B
In the sequential investigation of patients with moderate to high pre-test risk with previous testing for ischemia for more than two years	IIa	B
In the assessment of asymptomatic patients after incomplete revascularization	IIa	C
In the evaluation of symptomatic patients after revascularization	IIa	B
Routine reassessment (every five years) in asymptomatic patients after revascularization	IIb	C
As an initial method in the assessment of patients with low pre-test probability and with clinical conditions and interpretable electrocardiogram to perform an ergometric test	III	C
In the preoperative assessment of non-cardiac intermediate-risk surgery in patients with functional class ≥ 4 METs	III	B
Routine ergometric test substitution in patients with physical capacity and interpretable electrocardiogram for the performance of the test	III	C

MET: metabolic equivalent of risk.

weapon for adequate visualization of the endocardium of all LV segments.^{185,190} Thus, in the presence of two or more contiguous segments with limited technical quality, the use of any of these agents is indicated (Table 38).^{191,192} The use of contrast agents for myocardial perfusion, although it is part of the same procedure, only with modifications in the acquisition and analysis of the images, remains considered off-label by the US and European health agencies. Guidelines on stable coronary disease already recognize the use of contrast agents to delineate endocardial borders, but they are still not based on myocardial perfusion evaluation.¹⁷⁵ However, robust evidence supports the use of these agents for assessing myocardial perfusion both in the diagnosis of coronary disease in acute and chronic coronary syndromes,¹⁹³ even showing its superiority over conventional stress echocardiography in predicting cardiovascular events.¹⁹⁴ The accuracy of contrast agents has been compared with other methods such as myocardial scintigraphy and, in contrast, showed similarity, with greater sensitivity, mainly in the detection of uni-coronary lesions.¹⁹⁵ However, the use of contrast agents for perfusion analysis is facilitated when stress is performed with dipyridamole; and the low use of dipyridamole in most Brazilian and worldwide

echocardiography laboratories¹⁹² may be a barrier to the implementation of myocardial perfusion analysis.

Coronary flow reserve can also be assessed by contrast echocardiography under stress. Reduced values of coronary flow reserve are indicative of functional reperfusion in lesions that anatomically have dubious expression. In addition, some studies have shown the role of this index in assessing viability and in predicting myocardial functional recovery in patients with stable coronary artery disease.¹⁹⁶

6. Evaluation of Emboligenic Sources and Cardioembolic Diseases

Stroke is the major cause of disability and the second leading cause of death in the world.¹⁹⁷ Brazil is the Latin American country with the highest mortality rates due to stroke, being the main cause of female death.^{198,199} Although the death rate from stroke has declined in recent decades, the values remain very high.²⁰⁰ It is estimated that cardioembolic disease is responsible for 15% to 40% of all causes of ischemic stroke,²⁰¹ whereas indeterminate (cryptogenic) causes account for 30 to 40% of these ischemic neurological events.²⁰²⁻²⁰⁴ Other causes of ischemic

Statement

Table 38 – Recommendations for the use of echocardiographic contrast agents in chronic coronary disease

Recommendation	Class of recommendation	Level of evidence
Improvement of endocardial border delineation and analysis of global or regional ventricular function when endocardial visibility in two or more segments is limited	I	B
Myocardial perfusion analysis in the diagnosis of chronic coronary disease, both in the assessment of ischemia and viability as an adjunct to the modalities of stress echocardiography	IIa	B
Assessment of the coronary flow reserve in the study of the functional repercussion of already known or viable coronary lesions	IIa	B
Use in the presence or suspected of significant intracardiac shunts	III	B
Routine use of contrast in patients whose image and endocardial edge delineation of the left ventricle are of adequate quality	III	C

stroke include large artery atherosclerosis, small vessel occlusion (lacunar), and other etiologies.²⁰⁵ In patients who are at risk or who have already had embolic neurologic events, the main role of echocardiography is to identify the presence of an emboligenic source, to determine the probability of such a source being a possible cause of ischemic stroke or systemic embolism and to guide the therapy of these patients. We can classify cardiac diseases as for their emboligenic potential under high and low risk conditions (Table 39). The main causes of ischemic stroke of cardioembolic origin are: atrial fibrillation, associated or not with rheumatic MS (five-fold risk of stroke); left ventricular dysfunction (two to three times greater risk of ischemic stroke than the general population);²⁰⁶ acute myocardial infarction (the risk is possibly decreasing by the implementation of early reperfusion therapies);²⁰⁷ mechanical valvular prostheses (annual risk of ischemic stroke at 4.0%);²⁰⁸ and infectious endocarditis (one in five cases are complicated by ischemic stroke).²⁰⁹ Variable rates of annual recurrence of ischemic stroke have been reported in patients with aortic arch atheroma (less than 3 to 12%).²¹⁰ The patent foramen ovale (PFO) can serve as a passageway from a paradoxical embolism of the venous to the arterial circulation. Although patients with an ischemic stroke of indeterminate (cryptogenic) etiology have a higher incidence of FOP than those with known ischemic stroke cause,²¹¹ a large study reported that the presence of a PFO was not associated with an increased risk of recurrence of ischemic stroke.²¹² Other more rare causes of embolism include papillary fibroelastoma, myxoma, and mitral calcification.

The cardioembolic etiology of ischemic stroke should be suspected in the presence of severe onset of early neurologic deficit without prodromes, multiple brain lesions in multiple vascular territories, and recurrent ischemic stroke in a short period of time.²¹³ Systemic embolization to other organs such as spleen and kidneys at the time of the ischemic stroke increases the suspicion of cardioembolic etiology.²¹³ TTE and/or TEE should be recommended in patients with suspected cardiac embolic source, including ischemic stroke and transient ischemic attack (TIA) or systemic embolism. TTE is more suitable for evaluation of embolic sources present in previous cardiac structures, such as the apical thrombus

Table 39 – Classification of cardiac diseases regarding their emboligenic potential

High risk	Low risk
Intracavitary thrombus	Patent foramen ovale
Atrial fibrillation	Interatrial septum aneurysm
Acute myocardial infarction	Interatrial communication
Dilated cardiomyopathies	Spontaneous contrast
Infectious endocarditis	Lambl excrescences
Valve prostheses	Mitral valvular calcification
Rheumatic mitral stenosis	Aortic valve calcification
Left atrial myxoma	Endocarditis marantica
Papillary fibroelastoma	Mitral valve prolapse
Ulcerated plaques in the aorta	

investigation of the left ventricle. In contrast, during the TEE, the transducer is positioned in the esophagus, and the probe is closer to the posterior heart structures. The esophagus is also adjacent to the LA, so TEE corresponds to the gold standard examination for thrombus screening in the left atrial appendix, with sensitivity and specificity approaching 99%. TEE should be recommended as an initial diagnostic tool in the assessment of cardiac embolic source in patients with ischemic stroke, especially in those where the therapeutic decision (anticoagulation or cardioversion) will depend on the echocardiographic findings. TEE should also be recommended when TTE imaging is of poor quality in young patients with ischemic stroke, in patients with ischemic stroke of undetermined etiology, and in those with non-lacunar ischemic stroke. TTE may not be useful when TEE is already programmed for TEE, such as in the evaluation of intracardiac masses, prosthetic heart valves, the thoracic aorta, or to guide percutaneous procedures. TEE should not be recommended when TTE findings are compatible with the embolic cardiac source. Both TTE and TEE should not be recommended in patients whose results will not guide the therapeutic decision. Table 40 lists the main recommendations of TTE and/or TEE in patients with TIA, ischemic stroke or systemic embolism.

Table 40 – Recommendations of the echocardiography in the evaluation of emboligenic sources and cardioembolic diseases

Recommendation	Class of recommendation	Level of evidence
Suspected cardiac embolic source, including ischemic stroke and TIA or systemic embolism	I	C
Young patient (< 45 years) with TIA or acute ischemic stroke	I	C
Elderly patient with evidence of non-lacunar ischemic stroke	I	C
TIA or cryptogenic ischemic stroke	I	C
TEE as the initial test to facilitate clinical decision-making regarding treatment (anticoagulation or cardioversion)	I	B
Assessment of cardiac emboligenic source when non-cardiac origin has been previously identified	IIb	C
TTE when TEE is already programmed (e.g. in the evaluation of intracardiac masses, prosthetic heart valves, thoracic aorta, or to guide percutaneous procedures)	IIb	C
TEE when TTE findings are diagnostic of cardiac embolic sources	III	C
TTE and/or TEE results do not guide the therapeutic decision	III	C

TIA: transient ischemic attack; TEE: transesophageal echocardiography; TTE: transthoracic echocardiography.

7. Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac arrhythmia, whose prevalence increases with advancing age.^{214,215} In the United States, it is estimated that the prevalence of atrial fibrillation will double from 5.2 million cases in 2010 to 12.1 million cases in 2030.²¹⁶ In addition to population aging, the increased prevalence of AF can be explained by the comorbidities and associated cardiovascular risks such as hypertension, heart failure, coronary artery disease, valve diseases, obesity and diabetes mellitus.²¹⁷ The risk of developing AF is 1 in 4 individuals from 40 years of age on.²¹⁸ Recent national and international guidelines have reported the classification of AF based on its presentation, duration and spontaneous termination of AF episodes.^{214,219,220} Paroxysmal AF is defined as that which is reversed spontaneously or with medical intervention until seven days after its initiation. Episodes lasting longer than seven days are referred to as persistent AF. Persistent long-term AF represents cases lasting more than one year. Permanent AF corresponds to the cases in which attempts to revert to sinus rhythm will no longer be instituted. Finally, non-valvular AF is defined as AF in the absence of rheumatic MS, mechanical or biological valve or previous mitral valve repair. As part of the initial evaluation, all AF patients should have a TTE to identify structural heart diseases, including valvular heart disease, assess RA and LA size, LV and RV size and function.¹⁸⁴ TEE is the most sensitive and specific technique for detecting intracavitary thrombi, especially in the left atrial appendage, as a potential source of systemic embolism in AF, and can be used to guide early cardioversion or catheter ablation procedures.^{214,220,221} TEE can also identify features associated with an increased risk of thrombus formation in LA, including reduced flow velocity in the left atrial appendage, spontaneous contrast in LA, and aortic atheroma.²¹⁴ Table 41 lists the main recommendations of TTE and/or TEE in patients with AF. Although the echocardiography provides important information for assessing the likelihood of achieving successful rhythm control after cardioversion, including atrial size, left ventricular systolic function, and severity of valve disease,

randomized trials with a larger sample size are still lacking to understand the real prognostic value of imaging techniques in patients with AF.²²² New echocardiographic techniques such as LA evaluation by strain and 3D echocardiography are promising tools for future clinical practice.²²²

8. Heart Tumors and Masses

The cardiac masses comprise a broad set of lesions which may be neoplastic and non-neoplastic in nature. As regards incidence, the most frequent causes of cardiac masses are thrombi and vegetation, and rarely are tumors and pseudotumors (intrinsic and extrinsic structures that mimic a cardiac tumor).²²³ Cardiac tumors are extremely rare, with secondary tumors (metastatic neoplasms) being 20 times more frequent than primary tumors.^{224,225} Although the classification of these lesions for benignity or malignancy is an important predictor of prognosis, any cardiac tumor may have substantial hemodynamic or electrical consequences depending on size and location.²²⁶ Most are detected incidentally during cardiac imaging tests or after complementary evaluation of specific clinical situations, such as after embolic event, suspected endocarditis and the possibility of malignancy involving the heart. Myxomas are the most frequent benign primary tumors in adults, followed by fibroelastomas and, finally, fibromas (much more common in the pediatric population). Primary malignant tumors, however, represent a much smaller portion of primary cardiac neoplasms, with sarcomas and lymphomas being more common. Much more frequent, as mentioned above, are secondary tumors, represented by metastases, which can occur by various forms of dissemination (hematogenous, contiguous, venous and lymphatic), associated mainly to tumors of the breast, lung, esophagus, mediastinum and melanoma. In these cases, the involvement of the pericardium occurs most of the time.²²⁷

Echocardiography, because of its availability and applicability, is the imaging technique commonly chosen for diagnosis (Table 42). The examination may delineate the multiple cardiac structures and characteristics of a mass,

Statement

Table 41 – Recommendations of echocardiography in patients with atrial fibrillation

Recommendation	Class of recommendation	Level of evidence
TTE in the initial assessment of all patients with AF to identify structural heart disease and guide treatment	I	C
TTE in patients with AF lasting ≥ 48 hours to decide early cardioversion with brief heparinization, without previous oral anticoagulation	I	B
TEE in the assessment of patients before ablation or percutaneous occlusion of the left atrial appendage	I	B
Patient with AF requiring emergency cardioversion due to hemodynamic instability	III	C

TTE: transthoracic echocardiography; AF: atrial fibrillation; TEE: transesophageal echocardiography.

such as location, mobility, morphology, size, insertion site, and potential hemodynamic consequences. It also allows for serial images over time without the need for contrast agents (iodine or gadolinium) or radiation. New techniques, such as the 3D modality, by providing additional anatomical data are capable of increasing the diagnostic accuracy of the method, assisting in the surgical strategy, as well as monitoring immediate and late results of the procedure.^{228,229}

The contrasted echocardiographic study represents a very useful tool, offering greater anatomical detail and assisting in the differentiation of the masses through the analysis of its vascularization (hypervascularization is frequently associated with the presence of malignancy).²³⁰

9. Pericardial Diseases

Echocardiography should be indicated in the suspicion of pericardial affections, including (but not only) pericardial effusion, pericardial mass, constrictive pericarditis, effusive-constrictive pericarditis, patients after cardiac surgery and suspicion of cardiac tamponade (Table 43).^{231,232} It contributes decisively to the semiquantitative evaluation of the pericardial effusion and its hemodynamic repercussion (depending on the volume and the velocity of the collected fluid), as well as exploring the underlying etiology, whether primary (e.g. pericarditis, chylothorax) or secondary (e.g. bleeding,

metastasis, myxedema, hydropericardium). The method provides information about the nature of the fluid, suggesting the presence of fibrin, clot, tumor, air, and calcium. The size of the effusion may be classified by the diastolic measurement of the echo-free pericardial space, as of small (< 10 mm), moderate (10 to 20 mm) and large (> 20 mm).²³³ Findings indicative of cardiac compression may precede the clinical manifestations of the tamponade and configure an emergency situation. In this context, pericardial puncture guided by echocardiography may alleviate hemodynamic impairment and save lives.²³³ Such procedure can be performed safely in centers with experience, avoiding radiation associated with fluoroscopy and/or cost of surgery, which makes pericardiocentesis guided by echocardiography the procedure of choice.²³⁴ Individuals with chronic or recurrent pericardial effusion, not responsive to the proposed clinical treatment, may be referred for elective pericardial drainage after serial evaluation. The spectrum of echocardiography utilization in pericardial disease also includes congenital defects, trauma, neoplasia, cysts, CT after radiotherapy and the differential diagnosis between constrictive pericarditis and restrictive cardiomyopathy. In this differentiation, findings compatible with constriction are: exacerbated decrease (> 25%) in the E-wave velocity of the mitral flow in the first beat after inspiration, normal tissue Doppler mitral annular velocity ($e' > 7$ cm/s) and annulus paradoxus (e' septal > e' lateral).²³³

Table 42 – Recommendations of the echocardiography in patients with intracardiac masses and tumors

Recommendation	Class of recommendation	Level of evidence
Assessment of individuals with clinical suspicion (signs and symptoms) or patients with conditions predisposing to cardiac tumors	I	C
Carriers of malignant neoplasia with high risk of cardiac involvement	I	C
Evolutionary follow-up after surgical removal of cardiac tumors with high potential for recurrence (such as myxomas)	I	C
TTE for complementary anatomical and functional assessment in cases in which TTE was not definitive	I	C
TEE for complementary intraoperative assessment	I	C
3D echocardiography to search for additional anatomical information not seen in 2D TTE	I	C
Use of echocardiographic contrast for differential diagnosis and vascularization analysis	IIa	B
Patients with direct relatives with family history of myxoma	IIa	B
Patients whose results of the examination findings will not imply in therapeutic decision	III	C

TEE: transesophageal echocardiography; TTE: transthoracic echocardiography; 3D: three dimensional; 2D: two dimensional.

Table 43 – Recommendations of the echocardiography in pericardial diseases

Recommendation	Class of recommendation	Level of evidence
Clinical suspicion of pericardial effusion	I	C
Serial studies for evaluation of recurrent stroke	I	C
Assessment after radiotherapy (five years in patients at high risk for cardiotoxicity and ten years in others)	I	C
Suspicion of constrictive pericarditis, early detection of constriction or differential diagnosis with restriction	I	B
Suspected cardiac tamponade (chest trauma, cardiac surgery, iatrogenic perforation in cardiac catheterization or electrophysiological study, rupture of the ventricular wall after myocardial infarction and aortic dissection)	I	C
Suspected pericardial cyst, pericardial mass or pericardial agenesis	I	C
Monitoring of pericardiocentesis	I	B
Serial studies to assess the effect of treatment on stroke	IIa	C
Routine examination for small effusions in hemodynamically stable patients	III	C
Investigation of pericardial thickening without reperussion	III	C

10. Systemic Diseases

10.1. Introduction

The indication of echocardiography in systemic diseases depends on the prevalence of associated heart disease, the characteristics peculiar to cardiac involvement in each situation and the clinical suspicion of cardiac involvement.²³⁵ For example, examination is mandatory in individuals with systemic diseases potentially causing restrictive cardiomyopathy that show signs and symptoms of heart failure in clinical evolution. Some systemic diseases for which the indication of the examination should be considered are as follows.

10.2. Chronic Renal Failure

Morphophysiological changes in LV (such as hypertrophy, dilatation, systolic and diastolic dysfunction) are common in patients with end-stage renal disease and predict a worse prognosis.²³⁶⁻²³⁸ International guidelines recommend TTE for all dialysis patients one to three months after the initiation of renal replacement therapy and at three-year intervals thereafter, despite the symptoms.²³⁹

10.3. Amyloidosis

It is a common cause of restrictive cardiomyopathy and may be familial (transthyretin) or nonfamilial (primary or light chain). Cardiac involvement due to amyloid deposition may lead to some suggestive echocardiographic findings: thickening and increased echogenicity ("granular" appearance) of the LV walls (especially in the absence of arterial hypertension), biatrial dilatation, thickening of the valves and interatrial septum, diastolic dysfunction (grade II and III), small pericardial effusion, prominent decrease in longitudinal strain in the basal and mid LV segments ("sparing" the apical segments), and later systolic dysfunction with LVEF.²⁴⁰

10.4. Sarcoidosis

It is important to investigate the presence of cardiac involvement in sarcoidosis (granulomatous disease of unknown origin), as this is a potentially fatal condition. Among the various echocardiographic findings that may be found, we have: dilated cardiomyopathy, restrictive cardiomyopathy, segmental contractility alterations that do not obey the classic coronary territorial distribution, basal septum akinesia, inferolateral aneurysm and abnormal thickness of the septum (thickening or thinning).²⁴¹

10.5. Neoplasias

The echocardiography can detect silent pericardial metastases in some types of neoplasia (such as breast and lung) and monitor the cardiotoxic effect of chemotherapeutic agents.²⁴²

10.6. Autoimmune Diseases

The test may diagnose lupus-associated cardiac manifestations, such as pericardial effusion and sterile vegetations, systemic sclerosis, such as pulmonary hypertension, or rheumatoid arthritis, such as valve abnormalities.²³⁵

11. Diseases of The Aorta, Pulmonary Artery and Veins

11.1. Aorta

The evaluation of the aorta is routine in the TTE, since it allows to examine some of its segments, mainly the aortic root and the proximal portion of the ascending aorta, affected in numerous affections. The root of the aorta is formed by the aortic ring, the sinuses of Valsalva and the synotubular junction. The descending aorta and the proximal abdominal aorta can be evaluated at the suprasternal and subxiphoid sections, respectively.^{154,243} However, the TTE should be considered a screening test, with limitations, since it does

Statement

not allow the analysis of all segments of the aorta, such as the aortic arch and the distal descending. In this case, it is necessary to use other imaging methods such as TEE, computed tomography or magnetic resonance imaging.^{154,243} The TEE allows the realization of excellent resolution images due to the proximity of the esophagus to the thoracic aorta. Despite the multiplanar sections offered, a small segment of the ascending aortic junction with the aortic arch is not visualized due to the interposition of the trachea.¹⁵⁴ The precise diagnosis of acute aortic syndromes, such as aortic dissection, intramural hematoma, penetrating ulcer and rupture of aortic aneurysms, is fundamental in the therapeutic strategy to be adopted. In unstable patients with suspected acute aortic syndrome, the imaging modality chosen will depend on local availability and expertise. In general, TTE is performed as an initial investigation (class I), complemented with TEE and/or tomography (both class I). The TEE shows good accuracy, mainly in the exclusion of artifacts caused by reverberations of the anterior wall of the LA and the pulmonary artery.²⁴⁴ Depending on the clinical suspicion, the diagnostic investigation should proceed with two or more imaging examinations due to the possibility of false negatives.²⁴⁵

11.2. Pulmonary Artery

The trunk of the pulmonary artery and the initial portion of the pulmonary branches can be assessed by TTE. TEE is more accurate, allowing a greater examination of the pulmonary artery and its branches, which allows a better appreciation of thrombi in the proximal territory of the pulmonary artery. Dilations of these vessels can also be diagnosed. Pulmonary artery dilations are uncommon lesions and may be associated with different etiologies, such as congenital heart diseases, systemic vasculitis, collagenosis, infections and traumas.

11.3. Veins

Anomalies of the superior and inferior vena cava can be diagnosed by TTE and/or TEE. The presence of thrombi in these pathways and the extension of tumors into the right cavities can be evaluated. TEE is particularly useful for the identification of thrombus or vegetation in the superior vena cava in patients with long-stay catheters and in cases of pulmonary vein stenosis after AF or atrial flutter ablation procedures. The persistence of the left superior vena cava should be suspected in the presence of dilated coronary sinus and the diagnosis can be made using intravenous injection of agitated saline solution, which will first contrast the coronary sinus and then the right cavities. In this case, it is important to emphasize the need to exclude anomalous drainage of the left pulmonary vein via the vertical vein.²⁴⁶

12. Intraoperative Echocardiography in Cardiac and Non-Cardiac Surgeries

12.1. Introduction

Intraoperative echocardiography is a technique for monitoring cardiac and non-cardiac surgeries that allows a rapid and real-time assessment of anatomic and functional

cardiac features (global and segmental function, valvular function, volume and vascular resistance), aortic and phenomena with embolic potential.^{247,248} In non-cardiac surgeries, clinical information obtained by intraoperative echocardiography is often complementary to data provided by other hemodynamic monitoring devices (e.g., central venous catheter, pulmonary artery catheter, or arterial line).^{247,249} In the case of cardiovascular surgeries, the intraoperative echocardiography can also contribute with real-time dynamic information and images of the cardiac structures to plan, guide and evaluate the immediate result of the surgical intervention.²⁵⁰

12.2. Modalities of Intraoperative Echocardiography

A) Transesophageal: most widely used in open, minimally invasive or percutaneous cardiac surgeries, as well as in non-cardiac surgeries. It has the advantage of not entering the sterile field and of not disturbing the surgical procedure, allowing continuous monitoring. It is a relatively safe modality when performed by properly trained professionals. The contraindications are the same as for the conventional TEE. In young children, the use of intraoperative TEE should be considered on a case-by-case basis, based on the unique risks of these patients (e.g., bronchial obstruction).²⁴⁸

B) Epicardial or epiaortic: are an alternative for monitoring open heart surgeries in which there is absolute or relative contraindication of manipulation of the esophagus, or blood dyscrasia. In these embodiments, the linear or sectoral transducer is wrapped in a sterile cap and applied directly over the heart or aorta. The epiaortic technique is a very important tool in patients with advanced atheromatous disease, since it allows the choice of a suitable site for cannulation and aortic clamping.²⁴⁹

C) Transthoracic: may be considered as a monitoring alternative for percutaneous or non-cardiac procedures that are performed with superficial sedation, or in cases in which the patient has absolute or relative contraindication of esophageal manipulation. In this modality, the examination can be performed serially during the procedure, or at specific times as needed (e.g., in cases of hemodynamic instability, to guide endomyocardial biopsy).

D) Intracavitary: little used, more restricted to percutaneous procedures.

12.3. Recommendations in Cardiac and Thoracic Aorta Surgery

The main objectives of the use of intraoperative echocardiography in cardiac and thoracic aorta surgeries are: to confirm and refine the preoperative diagnosis; to detect new or unsuspected morphophysiological alteration; adjusting the surgical or anesthetic plane according to the findings; to guide the positioning of cannulae or devices; to evaluate the presence of air, masses and thrombi in cardiac cavities and their embolic potential; to evaluate segmental and global left ventricular function and cavitory pressures; and to evaluate the immediate outcome of the intervention.^{244,245,249} The main recommendations in this scenario are in the Table 44.

Table 44 – Recommendations of the intraoperative echocardiography in cardiac and thoracic aorta surgeries

Recommendation	Class of recommendation	Level of evidence
Adults submitted to cardiac or thoracic aorta open-chest surgery (e.g., valve plasty replacement, structural, mass resection, correction of aortic dissection or aortic aneurysm)	I	B
Adults undergoing minimally invasive cardiac surgery	I	B
In young children undergoing open or minimally invasive cardiac surgery, the indication should be considered case by case according to the risks of intraoperative echocardiography in the pediatric population (e.g., bronchial obstruction)	I	B
Placement and adjustment of ventricular assist devices	I	B
Myocardial revascularization surgery when there is left ventricular systolic dysfunction	IIa	B
In case there is a trained professional available, three-dimensional echocardiography should always be used for valvular (aortic and mitral regurgitation), structural and mass resection procedures	I	B

12.4. Recommendations in Non-Cardiac Surgeries

The main objectives of intraoperative echocardiography in non-cardiac surgeries are: to assess volume status and fluid response; to estimate vascular resistance and cavitory pressures; to evaluate function of the ventricles (global and segmental) and valves; and to investigate special issues according to the clinical status and the type of intervention.^{244,245,249} The main recommendations in this scenario are found in Table 45.

13. Echocardiography in Percutaneous Interventions

13.1. Introduction

In general, cardiac interventions through cardiac catheterization have developed with the support of the echocardiographic image, especially by the transesophageal route. Its use in daily practice is increasingly frequent, in view of the development of techniques and technologies for the treatment of diseases previously only corrected by the conventional surgical procedure. In addition, there was remarkable progress in the diagnostic capacity of echocardiography, mainly due to the improvement of the

image quality and the advent of the 3D image, obtained by TTE and TEE. The examination has practically no contraindication and allows the early identification of potential complications. There is no randomized study for non-use of echocardiography during procedures, and some are limited to the use of thoracic, esophageal or intracardiac modalities. Therefore, in relation to interventional procedures, indication of echocardiography use is in principle class I, level of evidence C, a fact already recognized in the literature.²³⁴ In some examinations, it becomes necessary as well as essential, since the X-ray (XR) image is insufficient to perform the procedure, and sometimes even expendable. The role of echocardiography in major interventional procedures follows below.

13.2. Follow-up of Interventions in Congenital Heart Diseases

A) Atrial septostomy: also known as Rashkind procedure. The septostomy is performed by balloon in a population in which the TTE allows an optimal visualization of the atrial septum and of the catheter, guiding in an appropriate way and evaluating the immediate result and eventual complications. The use of TEE is usually unnecessary, and also impracticable,

Table 45 – Recommendations of the intraoperative echocardiography in non-cardiac surgeries

Recommendation	Class of recommendation	Level of evidence
Intraoperative echocardiography may be indicated for the monitoring of non-cardiac surgeries if the patient is suffering from severe cardiovascular disease and/or the planned procedure may result in severe hemodynamic, myocardial, pulmonary or neurological impairment	I	B
Large vascular surgery (usually in open abdominal aortic repair surgeries)	I	B
Liver transplantation	IIa	B
Pulmonary transplantation	IIa	B
Renal tumor resection	IIb	B
Surgery of trauma	IIb	B
Neurosurgery	IIa	B
Orthopedic Surgeries	IIb	B
Laparoscopic surgeries	IIb	B

Statement

due to the lack of adequate probes. In this case, even the XR scoping can be discarded.

B) Procedures for occlusion of atrial septal defects: there are devices for occlusion of defects of the atrial septal defect, ostium secundum, as well as patent foramen ovale. The examination can be performed in both, mainly TEE or intracardiac echocardiography, where it is possible to assist in the choice of the device, its positioning, immediate result and rapid identification of complications. TTE may be preferable to TEE in selected patients.²⁵¹

C) Procedures for occlusion of ventricular septal defects: TEE should be performed to better understand the anatomical aspects, the procedure itself and possible complications. Acquired ventricular septum defects, such as those after trauma or after acute infarction, may also be treated with the aid of echocardiography, presenting the same value in the procedure.

D) Procedures for occlusion of ductus arteriosus persistence: in this situation, echocardiography is disregarded, since catheterization during the procedure is usually sufficient for success.

13.3. Electrophysiology Procedures

The echocardiography mainly supports the procedure of puncture of the atrial septum, usually through TEE, or alternatively by intracardiac echocardiography. In the procedure of ablation or implantation of pacemaker the echocardiography is dispensable, since the electrical mapping provides the necessary information. In the presence of complications, such as perforation of a chamber with pericardial effusion and tamponade, the echocardiography is normally requested.

13.4. Alcoholic Ablation in Hypertrophic Cardiomyopathy

One of the treatments for symptomatic patients consists of alcohol ablation of the segment where there is a greater degree of hypertrophy and related to intraventricular obstruction in its exit pathway. TTE is more used, and there is no restriction on the use of TEE. Prior to alcohol infusion, the septal artery is catheterized and a solution is infused. At this time, the echocardiography should assess whether the contrast-enhanced myocardial segment corresponds to the portion of the myocardium associated with the obstruction and if it does not occur in all transmurality of the segment, which is undesirable. The Doppler study estimates the gradient of obstruction and also the degree of mitral regurgitation. After alcoholic ablation, we repeat the measurement of gradients and mitral regurgitation, whose falls indicate successful treatment, and possible complications are investigated.

13.5. Left Atrial Appendage Occlusion

An alternative, when it is impossible to carry out adequate anticoagulation in patients at high risk for atrial arrhythmia embolism, is occlusion of the left atrial appendage. TEE is mandatory in this treatment, as it not only helps the transseptal puncture, but also allows adequate appendage measurements, which select the dimensions of the occluder

device. Still in the room, the TEE guides the procedure, confers its result and makes it possible to diagnose complications.

13.6. Treatment of Heart Valves

A) Percutaneous treatment of mitral regurgitation: among the several treatments proposed, the only one that is commercially available is Mitraclip®. In this treatment there is a mimicry of the Alfieri surgery, where there is the formation of a double mitral orifice. To do so, a metallic clip is inserted through the vein, which advances to the LA after puncture of the atrial septum and is positioned so as to reduce severe mitral regurgitation. In this case, no step is performed without the TEE, considering that the 3D image provides better understanding of the procedure.

B) Balloon catheter mitral valvotomy: the use of balloons for the treatment of severe rheumatic mitral stenosis is a safe and efficient alternative. The echocardiography prior to the procedure provides information that can predict the chance of success.^{252,253} In the intervention, the TEE is preferable, and the morphological aspects of the mitral valve should be reviewed. During the inflation of the balloon (or balloons), the echocardiography allows to detect proper positioning. Immediately after the procedure, measures are performed with the objective of evaluating the success of the procedure and the complications that may have occurred.

C) Balloon catheter aortic valvotomy: the use of this therapy is currently safeguarded as the last alternative for the treatment of aortic stenosis or as a bridge to compensate for the clinical condition and subsequent implantation of a prosthesis via cardiac catheterization or surgery. The echocardiography can be used to evaluate immediate results and complications.

D) Transcatheter implant of aortic valve prosthesis: the indication of the percutaneous implantation of aortic valve prosthesis is conditioned to clinical and morphological aspects of the aortic valve. It is necessary to diagnose severe aortic stenosis prior to the procedure, as well as the analysis of the aortic complex, which selects the size of the most appropriate device for the procedure, directly related to its success. The preference is for the use of TEE, especially with 3D image. During the procedure, it is necessary to review the severity of valve stenosis by measuring the gradients and estimating the effective flow orifice. Still, measurement of the aortic complex and especially of the area/perimeter of the aortic ring, performed only through the 3D echocardiography is necessary. The value obtained is optimally related to tomography measurements that are usually used to select the device.²⁵⁴ Whether femoral or transapical, monitoring of the arrival of the prosthesis to the aortic valve is performed, as well as the aid of the ideal positioning, prior to its opening. After implantation, the TEE should provide data on adequate prosthesis expansion, presence and degree of prosthetic and/or paraprosthesis regurgitation. Complications of the procedure are part of the echocardiography investigation.

13.7. Treatment of Prosthetic Dysfunction

A) Valve in valve: The term “valve in valve” means the implant of a prosthesis via a catheter over a dysfunctional bioprosthesis. It can be made in prostheses in aortic and mitral

position, the latter only by transapical way. The monitoring during the process of arrival of the prosthesis, its implant and the identification of complications must be done by the TEE.

B) Occlusion of paraprothetic regurgitation orifices: one of the possibilities of regurgitation in a valve prosthesis is the presence of paraprothetic orifices. TEE, especially 3D, should

be used to identify these orifices, locate them accurately, and measure their area and diameter to select the most appropriate occlusion device. In the procedure, the echocardiographic image helps to visualize the passage of the guiding catheters through the paraprothetic site, to open the device and to measure the success of the treatment.

References

- Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. *J Am Soc Echocardiogr*. 1989;2(5):358-67.
- Sahn DJ, DeMaria A, Kisslo J, Weyman A. Recommendations regarding quantitation in M-mode echocardiography: results of a survey of echocardiographic measurements. *Circulation*. 1978;58(6):1072-83.
- Teichholz LE, Kreulen T, Herman MV, Gorlin R. Problems in echocardiographic volume determinations: echocardiographic-angiographic correlations in the presence of absence of asynergy. *Am J Cardiol*. 1976;37(1):7-11.
- Lang RM, Badano LP, Mor-Avi V, Afzal J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(3):233-70.
- Yu CM, Lin H, Yang H, Kong SL, Zhang Q, Lee SW. Progression of systolic abnormalities in patients with "isolated" diastolic heart failure and diastolic dysfunction. *Circulation*. 2002;105(10):1195-201.
- Mor-Avi V, Jenkins C, Kuhl HP, Nesser HJ, Marwick T, Franke A, et al. Real-time 3-dimensional echocardiographic quantification of left ventricular volumes: multicenter study for validation with magnetic resonance imaging and investigation of sources of error. *JACC Cardiovasc Imaging*. 2008;1(4):413-23.
- Shimada YI, Shiota T. A meta-analysis and investigation for the source of bias of left ventricular volumes and function by three-dimensional echocardiography in comparison with magnetic resonance imaging. *Am J Cardiol*. 2011;107(1):126-38.
- Dorosio JL, Lezotte DC, Weitzkamp DA, Allen LA, Salcedo EE. Performance of 3-dimensional echocardiography in measuring left ventricular volumes and ejection fraction: a systematic review and meta-analysis. *J Am Coll Cardiol*. 2012;59(20):1799-808.
- Oliveira LF, O'Connell JL, Carvalho EE, Pulici EC, Romano MM, Maciel BC, et al. Comparison between Radionuclide Ventriculography and Echocardiography for Quantification of Left Ventricular Systolic Function in Rats Exposed to Doxorubicin. *Arq Bras Cardiol*. 2017;108(1):12-20.
- Vieira ML, Nomura CH, Tranchesi Junior B, Oliveira WA, Naccarato G, Serpa BS, et al. Left ventricular ejection fraction and volumes as measured by 3d echocardiography and ultrafast computed tomography. *Arq Bras Cardiol*. 2009;92(4):294-301.
- Vieira ML, Nomura CH, Tranchesi B, Jr., de Oliveira WA, Naccarato G, Serpa BS, et al. Real-time three-dimensional echocardiographic left ventricular systolic assessment: side-by-side comparison with 64-slice multi-detector cardiac computed tomography. *Eur J Echocardiogr*. 2010;11(3):257-63.
- Tsang W, Salgo IS, Medvedofsky D, Takeuchi M, Prater D, Weinert L, et al. Transthoracic 3D Echocardiographic Left Heart Chamber Quantification Using an Automated Adaptive Analytics Algorithm. *JACC Cardiovasc Imaging*. 2016;9(7):769-82.
- Amundsen BH, Helle-Valle T, Edvardsen T, Torp H, Crosby J, Lyseggen E, et al. Noninvasive myocardial strain measurement by speckle tracking echocardiography: validation against sonomicrometry and tagged magnetic resonance imaging. *J Am Coll Cardiol*. 2006;47(4):789-93.
- Korinek J, Wang J, Sengupta PP, Miyazaki C, Kjaergaard J, McMahon E, et al. Two-dimensional strain—a Doppler-independent ultrasound method for quantitation of regional deformation: validation in vitro and in vivo. *J Am Soc Echocardiogr*. 2005;18(12):1247-53.
- Thavandiranathan P, Poulin F, Lim KD, Plana JC, Woo A, Marwick TH. Use of myocardial strain imaging by echocardiography for the early detection of cardiotoxicity in patients during and after cancer chemotherapy: a systematic review. *J Am Coll Cardiol*. 2014;63(25 Pt A):2751-68.
- Du GQ, Hsiung MC, Wu Y, Qu SH, Wei J, Yin WH, et al. Three-Dimensional Speckle-Tracking Echocardiographic Monitoring of Acute Rejection in Heart Transplant Recipients. *J Ultrasound Med*. 2016;35(6):1167-76.
- Ersboll M, Valeur N, Mogensen UM, Andersen MJ, Møller JE, Velazquez EJ, et al. Prediction of all-cause mortality and heart failure admissions from global left ventricular longitudinal strain in patients with acute myocardial infarction and preserved left ventricular ejection fraction. *J Am Coll Cardiol*. 2013;61(23):2365-73.
- Sjoli B, Orn S, Grenne B, Vartdal T, Smiseth OA, Edvardsen T, et al. Comparison of left ventricular ejection fraction and left ventricular global strain as determinants of infarct size in patients with acute myocardial infarction. *J Am Soc Echocardiogr*. 2009;22(11):1232-8.
- Kearney LG, Lu K, Ord M, Patel SK, Profitis K, Matalanis G, et al. Global longitudinal strain is a strong independent predictor of all-cause mortality in patients with aortic stenosis. *Eur Heart J Cardiovasc Imaging*. 2012;13(10):827-33.
- Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2016;17(12):1321-60.
- Paulus WJ, Tschope C, Sanderson JE, Rusconi C, Flachskampf FA, Rademakers FE, et al. How to diagnose diastolic heart failure: a consensus statement on the diagnosis of heart failure with normal left ventricular ejection fraction by the Heart Failure and Echocardiography Associations of the European Society of Cardiology. *Eur Heart J*. 2007;28(20):2539-50.
- Barberato SH, Mantilla DE, Misocami MA, Goncalves SM, Bignelli AT, Riella MC, et al. Effect of preload reduction by hemodialysis on left atrial volume and echocardiographic Doppler parameters in patients with end-stage renal disease. *Am J Cardiol*. 2004;94(9):1208-10.
- Andersen OS, Smiseth OA, Dokainish H, Abudiyab MM, Schutt RC, Kumar A, et al. Estimating Left Ventricular Filling Pressure by Echocardiography. *J Am Coll Cardiol*. 2017;69(15):1937-48.

Statement

24. Lancellotti P, Pellikka PA, Budts W, Chaudhry FA, Donal E, Dulgheru R, et al. The clinical use of stress echocardiography in non-ischaemic heart disease: recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *Eur Heart J Cardiovasc Imaging*. 2016;17(11):1191-229.
25. Braunwald E. Cardiomyopathies: An Overview. *Cir Res*. 2017;121(7):711-21.
26. McKenna WJ, Maron BJ, Thiene G. Classification, Epidemiology, and Global Burden of Cardiomyopathies. *Circ Res*. 2017;121(7):722-30.
27. Hershberger RE, Hedges DJ, Morales A. Dilated cardiomyopathy: the complexity of a diverse genetic architecture. *Nat Rev Cardiol*. 2013;10(9):531-47.
28. Mathew T, Williams L, Navaratnam G, Rana B, Wheeler R, Collins K, et al. Diagnosis and assessment of dilated cardiomyopathy: a guideline protocol from the British Society of Echocardiography. *Echo Res Pract*. 2017;4(2):G1-13.
29. Jefferies JL, Towbin JA. Dilated cardiomyopathy. *Lancet*. 2010;375(9716):752-62.
30. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF, 3rd, Dokainish H, Edvardsen T, et al. Recommendations for the Evaluation of Left Ventricular Diastolic Function by Echocardiography: An Update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2016;29(4):277-314.
31. Abu Daya H, Alam MB, Adelstein E, Schwartzman D, Jain S, Marek J, et al. Echocardiography-guided left ventricular lead placement for cardiac resynchronization therapy in ischemic vs nonischemic cardiomyopathy patients. *Heart Rhythm*. 2014;11(4):614-9.
32. Acquatella H. Echocardiography in Chagas heart disease. *Circulation*. 2007;115(9):1124-31.
33. Nunes MC, Dones W, Morillo CA, Encina JJ, Ribeiro AL; Council on Chagas Disease of the Interamerican Society of C. Chagas disease: an overview of clinical and epidemiological aspects. *J Am Coll Cardiol*. 2013;62(9):767-76.
34. Nunes MC, Kreuser LJ, Ribeiro AL, Sousa GR, Costa HS, Botoni FA, et al. Prevalence and risk factors of embolic cerebrovascular events associated with Chagas heart disease. *Glob Heart*. 2015;10(3):151-7.
35. Nascimento CA, Gomes VA, Silva SK, Santos CR, Chambela MC, Madeira FS, et al. Left atrial and left ventricular diastolic function in chronic Chagas disease. *J Am Soc Echocardiogr*. 2013;26(12):1424-33.
36. Nunes MP, Colosimo EA, Reis RC, Barbosa MM, da Silva JL, Barbosa F, et al. Different prognostic impact of the tissue Doppler-derived E/e' ratio on mortality in Chagas cardiomyopathy patients with heart failure. *J Heart Lung Transplant*. 2012;31(6):634-41.
37. Barros MV, Leren IS, Edvardsen T, Haugaa KH, Carmo AA, Lage TA, et al. Mechanical dispersion assessed by strain echocardiography is associated with malignant arrhythmias in chagas cardiomyopathy. *J Am Soc Echocardiogr*. 2016;29(4):368-74.
38. Nunes MCP, Badano LP, Marin-Neto JA, Edvardsen T, Fernandez-Golfín C, Bucciarelli-Ducci C, et al. Multimodality imaging evaluation of Chagas disease: an expert consensus of Brazilian Cardiovascular Imaging Department (DIC) and the European Association of Cardiovascular Imaging (EACVI). *Eur Heart J Cardiovasc Imaging*. 2018;19(4):459-60n.
39. Yu CM, Bleeker GB, Fung JW, Schalij MJ, Zhang Q, van der Wall EE, et al. Left ventricular reverse remodeling but not clinical improvement predicts long-term survival after cardiac resynchronization therapy. *Circulation*. 2005;112(11):1580-6.
40. Stankovic I, Prinz C, Ciarka A, Daraban AM, Kotrc M, Aarones M, et al. Relationship of visually assessed apical rocking and septal flash to response and long-term survival following cardiac resynchronization therapy (PREDICT-CRT). *Eur Heart J Cardiovasc Imaging*. 2016;17(3):262-9.
41. Risum N, Tayal B, Hansen TF, Bruun NE, Jensen MT, Lauridsen TK, et al. Identification of Typical Left Bundle Branch Block Contraction by Strain Echocardiography Is Additive to Electrocardiography in Prediction of Long-Term Outcome After Cardiac Resynchronization Therapy. *J Am Coll Cardiol*. 2015;66(6):631-41.
42. Saba S, Marek J, Schwartzman D, Jain S, Adelstein E, White P, et al. Echocardiography-guided left ventricular lead placement for cardiac resynchronization therapy: results of the Speckle Tracking Assisted Resynchronization Therapy for Electrode Region trial. *Circ Heart Fail*. 2013;6(3):427-34.
43. Khan FZ, Virdee MS, Palmer CR, Pugh PJ, O'Halloran D, Elisk M, et al. Targeted left ventricular lead placement to guide cardiac resynchronization therapy: the TARGET study: a randomized, controlled trial. *J Am Coll Cardiol*. 2012;59(17):1509-18.
44. Ypenburg C, Van De Veire N, Westenberg JJ, Bleeker GB, Marsan NA, Henneman MM, et al. Noninvasive imaging in cardiac resynchronization therapy--Part 2: Follow-up and optimization of settings. *Pacing Clin Electrophysiol*. 2008;31(12):1628-39.
45. Bank AJ, Burns KV, Gage RM, Vatterott DB, Adler SW, Sajady M, et al. Cardiac resynchronization therapy in the real world: comparison with the COMPANION study. *J Card Fail*. 2012;18(2):153-8.
46. Mullens W, Borowski AG, Curtin RJ, Thomas JD, Tang WH. Tissue Doppler imaging in the estimation of intracardiac filling pressure in decompensated patients with advanced systolic heart failure. *Circulation*. 2009;119(1):62-70.
47. Badano LP, Miglioranza MH, Edvardsen T, Colafranceschi AS, Muraru D, Bacal F, et al. European Association of Cardiovascular Imaging/ Cardiovascular Imaging Department of the Brazilian Society of Cardiology recommendations for the use of cardiac imaging to assess and follow patients after heart transplantation. *Eur Heart J Cardiovasc Imaging*. 2015;16(9):919-48.
48. Costanzo MR, Dipchand A, Starling R, Anderson A, Chan M, Desai S, et al. The International Society of Heart and Lung Transplantation Guidelines for the care of heart transplant recipients. *J Heart Lung Transplant*. 2010;29(8):914-56.
49. Dandel M, Hetzer R. Post-transplant surveillance for acute rejection and allograft vasculopathy by echocardiography: Usefulness of myocardial velocity and deformation imaging. *J Heart Lung Transplant*. 2017;36(2):117-31.
50. Pieper GM, Shah A, Harmann L, Cooley BC, Ionova IA and Migrino RQ. Speckle-tracking 2-dimensional strain echocardiography: a new noninvasive imaging tool to evaluate acute rejection in cardiac transplantation. *J Heart Lung Transplant*. 2010;29(9):1039-46.
51. Stampfli SF, Ozkartal T, Hagenbuch N, Bernhart S, Flammer AJ, Vecchiati A, et al. Pericardial effusion unrelated to surgery is a predictor of mortality in heart transplant patients. *Cardiol J*. 2018;25(6):714-21.
52. Bacal F, Moreira L, Souza G, Rodrigues AC, Fiorelli A, Stolf N, et al. Dobutamine stress echocardiography predicts cardiac events or death in asymptomatic patients long-term after heart transplantation: 4-year prospective evaluation. *J Heart Lung Transplant*. 2004;23(11):1238-44.
53. Derumeaux G, Redonnet M, Mouton-Schleifer D, Bessou JP, Cribier A, Saoudi N, et al. Dobutamine stress echocardiography in orthotopic heart transplant recipients. VACOMED Research Group. *J Am Coll Cardiol*. 1995;25(7):1665-72.
54. Spes CH, Klauss V, Mudra H, Schnaack SD, Tammen AR, Rieber J, et al. Diagnostic and prognostic value of serial dobutamine stress echocardiography for noninvasive assessment of cardiac allograft vasculopathy: a comparison with coronary angiography and intravascular ultrasound. *Circulation*. 1999;100(5):509-15.
55. Sade LE, Eroglu S, Yuce D, Bircan A, Pirat B, Sezgin A, et al. Follow-up of heart transplant recipients with serial echocardiographic coronary

- flow reserve and dobutamine stress echocardiography to detect cardiac allograft vasculopathy. *J Am Soc Echocardiogr.* 2014;27(5):531-9.
56. Hacker M, Hoyer HX, Uebles C, Ueberfuhr P, Foerster S, La Fougere C, et al. Quantitative assessment of cardiac allograft vasculopathy by real-time myocardial contrast echocardiography: a comparison with conventional echocardiographic analyses and [Tc99m]-sestamibi SPECT. *Eur J Echocardiogr.* 2008;9(4):494-500.
 57. Rutz T, de Marchi SF, Roelli P, Gloekler S, Traupe T, Steck H, et al. Quantitative myocardial contrast echocardiography: a new method for the non-invasive detection of chronic heart transplant rejection. *Eur Heart J Cardiovasc Imaging.* 2013;14(12):1187-94.
 58. Tona F, Caforio AL, Montisci R, Gambino A, Angelini A, Ruscazio M, et al. Coronary flow velocity pattern and coronary flow reserve by contrast-enhanced transthoracic echocardiography predict long-term outcome in heart transplantation. *Circulation.* 2006;114(1 Suppl):I49-55.
 59. Tona F, Osto E, Tarantini G, Gambino A, Cavallini F, Feltrin G, et al. Coronary flow reserve by transthoracic echocardiography predicts epicardial intimal thickening in cardiac allograft vasculopathy. *Am J Transplant.* 2010;10(7):1668-76.
 60. Miller LW, Labovitz AJ, McBride LA, Pennington DG, Kanter K. Echocardiography-guided endomyocardial biopsy. A 5-year experience. *Circulation.* 1988;78(5 Pt 2):III99-102.
 61. Daher IN, Daigle TR, Bhatia N, Durand JB. The prevention of cardiovascular disease in cancer survivors. *Tex Heart Inst J.* 2012;39(2):190-8.
 62. Herrmann J, Lerman A, Sandhu NP, Villarraga HR, Mulvagh SL, Kohli M. Evaluation and management of patients with heart disease and cancer: cardio-oncology. *Mayo Clin Proc.* 2014;89(9):1287-306.
 63. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging.* 2014;15(10):1063-93.
 64. Armstrong GT, Plana JC, Zhang N, Srivastava D, Green DM, Ness KK, et al. Screening adult survivors of childhood cancer for cardiomyopathy: comparison of echocardiography and cardiac magnetic resonance imaging. *J Clin Oncol.* 2012;30(23):2876-84.
 65. Mor-Avi V, Lang RM. Is echocardiography reliable for monitoring the adverse cardiac effects of chemotherapy? *J Am Coll Cardiol.* 2013;61(1):85-7.
 66. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomini G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. *J Am Coll Cardiol.* 2010;55(3):213-20.
 67. Takigiku K, Takeuchi M, Izumi C, Yuda S, Sakata K, Ohte N, et al. Normal range of left ventricular 2-dimensional strain: Japanese Ultrasound Speckle Tracking of the Left Ventricle (JUSTICE) study. *Circ J.* 2012;76(11):2623-32.
 68. Pudil R, Horacek JM, Strasova A, Jebavy L, Vojacek J. Monitoring of the very early changes of left ventricular diastolic function in patients with acute leukemia treated with anthracyclines. *Exp Oncol.* 2008;30(2):160-2.
 69. Cardinale D, Sandri MT, Colombo A, Colombo N, Boeri M, Lamantia G, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation.* 2004;109(22):2749-54.
 70. Sawaya H, Sebag IA, Plana JC, Januzzi JL, Ky B, Tan TC, et al. Assessment of echocardiography and biomarkers for the extended prediction of cardiotoxicity in patients treated with anthracyclines, taxanes, and trastuzumab. *Circ Cardiovasc Imaging.* 2012;5(5):596-603.
 71. Curigliano G, Cardinale D, Suter T, Plataniotis G, de Azambuja E, Sandri MT, et al. Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Ann Oncol.* 2012;23(Suppl 7):vii155-66.
 72. Elliott PM, Anastakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). *Eur Heart J.* 2014;35(39):2733-79.
 73. Maron MS, Maron BJ, Harrigan C, Buys J, Gibson CM, Olivetto I, et al. Hypertrophic cardiomyopathy phenotype revisited after 50 years with cardiovascular magnetic resonance. *J Am Coll Cardiol.* 2009;54(3):220-8.
 74. Spirito P, Bellone P, Harris KM, Bernabo P, Bruzzi P, Maron BJ. Magnitude of left ventricular hypertrophy and risk of sudden death in hypertrophic cardiomyopathy. *N Engl J Med.* 2000;342(24):1778-85.
 75. Gersh BJ, Maron BJ, Bonow RO, Dearani JA, Fifer MA, Link MS, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Developed in collaboration with the American Association for Thoracic Surgery, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol.* 2011;58(25):e212-60.
 76. Biagini E, Spirito P, Rocchi G, Ferlito M, Rosmini S, Lai F, et al. Prognostic implications of the Doppler restrictive filling pattern in hypertrophic cardiomyopathy. *Am J Cardiol.* 2009;104(12):1727-31.
 77. Urbano-Moral JA, Rowin EJ, Maron MS, Crean A, Pandian NG. Investigation of global and regional myocardial mechanics with 3-dimensional speckle tracking echocardiography and relations to hypertrophy and fibrosis in hypertrophic cardiomyopathy. *Circ Cardiovasc Imaging.* 2014;7(1):11-9.
 78. Bharucha T, Lee KJ, Daubeney PE, Nugent AW, Turner C, Sholler GF, et al. Sudden death in childhood cardiomyopathy: results from a long-term national population-based study. *J Am Coll Cardiol.* 2015;65(21):2302-10.
 79. Risgaard B, Winkel BG, Jabbari R, Behr ER, Ingemann-Hansen O, Thomsen JL, et al. Burden of sudden cardiac death in persons aged 1 to 49 years: nationwide study in Denmark. *Circ Arrhythm Electrophysiol.* 2014;7(2):205-11.
 80. Maron BJ, Rowin EJ, Casey SA, Lesser JR, Garberich RF, McGriff DM, et al. Hypertrophic Cardiomyopathy in Children, Adolescents, and Young Adults Associated With Low Cardiovascular Mortality With Contemporary Management Strategies. *Circulation.* 2016;133(1):62-73.
 81. Elliott P, Andersson B, Arbustini E, Bilinska Z, Cecchi F, Charron P, et al. Classification of the cardiomyopathies: a position statement from the European Society Of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J.* 2008;29(2):270-6.
 82. Nihoyannopoulos P, Dawson D. Restrictive cardiomyopathies. *Eur J Echocardiogr.* 2009;10(8):iii23-33.
 83. Muchtar E, Blauwet LA, Gertz MA. Restrictive cardiomyopathy: genetics, pathogenesis, clinical manifestations, diagnosis, and therapy. *Circ Res.* 2017;121(7):819-37.
 84. Sun JP, Stewart WJ, Yang XS, Donnell RO, Leon AR, Felner JM, et al. Differentiation of hypertrophic cardiomyopathy and cardiac amyloidosis from other causes of ventricular wall thickening by two-dimensional strain imaging echocardiography. *Am J Cardiol.* 2009;103(3):411-5.
 85. Murtagh C, Laffin LJ, Patel KV, Patel AV, Bonham CA, Yu Z, et al. Improved detection of myocardial damage in sarcoidosis using longitudinal strain in patients with preserved left ventricular ejection fraction. *Echocardiography.* 2016;33(9):1344-52.
 86. Sen-Chowdhry S, Syrris P, Prasad SK, Hughes SE, Merrifield R, Ward D, et al. Left-dominant arrhythmogenic cardiomyopathy: an under-recognized clinical entity. *J Am Coll Cardiol.* 2008;52(25):2175-87.
 87. Qasem M, Utomi V, George K, Somauroo J, Zaidi A, Forsythe L, et al. A meta-analysis for echocardiographic assessment of right ventricular structure and function in ARVC. *Echo Res Pract.* 2016;3(3):95-104.

Statement

88. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, et al. Diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia:proposed modification of the Task Force Criteria. *Eur Heart J*. 2010;31(7):806-14.
89. Haugaa KH, Basso C, Badano LP, Bucciarelli-Ducci C, Cardim N, Gaemperli O, et al. Comprehensive multi-modality imaging approach in arrhythmogenic cardiomyopathy-an expert consensus document of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2017;18(3):237-53.
90. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies:an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee;Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups;and Council on Epidemiology and Prevention. *Circulation*. 2006;113(14):1807-16.
91. Paterick TE, Umland MM, Jan MF, Ammar KA, Kramer C, Khandheria BK, et al. Left ventricular noncompaction:a 25-year odyssey. *J Am Soc Echocardiogr*. 2012;25(4):363-75.
92. Chebrolu LH, Mehta AM, Nanda NC. Noncompaction cardiomyopathy:The role of advanced multimodality imaging techniques in diagnosis and assessment. *Echocardiography*. 2017;34(2):279-89.
93. Rosa LV, Salemi VM, Alexandre LM, Mady C. Noncompaction cardiomyopathy:a current view. *Arq Bras Cardiol*. 2011;97(1):e13-9.
94. Gati S, Rajani R, Carr-White GS, Chambers JB. Adult left ventricular noncompaction:reappraisal of current diagnostic imaging modalities. *JACC Cardiovasc Imaging*. 2014;7(12):1266-75.
95. Marwick TH, Gillebert TC, Aurigemma G, Chirinos J, Derumeaux G, Galderisi M, et al. Recommendations on the Use of Echocardiography in Adult Hypertension:A Report from the European Association of Cardiovascular Imaging (EACVI) and the American Society of Echocardiography (ASE). *J Am Soc Echocardiogr*. 2015;28(7):727-54.
96. McMullen JR, Jennings GL. Differences between pathological and physiological cardiac hypertrophy:novel therapeutic strategies to treat heart failure. *Clin Exp Pharmacol Physiol*. 2007;34(4):255-62.
97. Devereux RB. Is the electrocardiogram still useful for detection of left ventricular hypertrophy? *Circulation*. 1990;81(3):1144-6.
98. Liebson PR, Grandits G, Prineas R, Dianza S, Flack JM, Cutler JA, et al. Echocardiographic correlates of left ventricular structure among 844 mildly hypertensive men and women in the Treatment of Mild Hypertension Study (TOMHS). *Circulation*. 1993;87(2):476-86.
99. Lang RM, Badano LP, Mor-Avi V, Afzalalo J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults:an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr*. 2015;28(1):1-39 e14.
100. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Bohm M, et al. 2013 ESH/ESC Guidelines for the management of arterial hypertension:the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J Hypertens*. 2013;31(7):1281-357.
101. Kishi S, Teixido-Tura G, Ning H, Venkatesh BA, Wu C, Almeida A, et al. Cumulative Blood Pressure in Early Adulthood and Cardiac Dysfunction in Middle Age:The CARDIA Study. *J Am Coll Cardiol*. 2015;65(25):2679-87.
102. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults:a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2010;56(25):e50-103.
103. Koren MJ, Devereux RB, Casale PN, Savage DD, Laragh JH. Relation of left ventricular mass and geometry to morbidity and mortality in uncomplicated essential hypertension. *Ann Intern Med*. 1991;114(5):345-52.
104. Verdecchia P, Carini G, Circo A, Dovellini E, Giovannini E, Lombardo M, et al. Left ventricular mass and cardiovascular morbidity in essential hypertension:the MAVI study. *J Am Coll Cardiol*. 2001;38(7):1829-35.
105. Hogg K, Swedberg K, McMurray J. Heart failure with preserved left ventricular systolic function;epidemiology, clinical characteristics, and prognosis. *J Am Coll Cardiol*. 2004;43(3):317-27.
106. Sharp AS, Tapp RJ, Thom SA, Francis DP, Hughes AD, Stanton AV, et al. Tissue Doppler E/E' ratio is a powerful predictor of primary cardiac events in a hypertensive population:an ASCOT substudy. *Eur Heart J*. 2010;31(6):747-52.
107. Galderisi M, Lomoriello VS, Santoro A, Esposito R, Olibet M, Raia R, et al. Differences of myocardial systolic deformation and correlates of diastolic function in competitive rowers and young hypertensives:a speckle-tracking echocardiography study. *J Am Soc Echocardiogr*. 2010;23(11):1190-8.
108. Saito M, Khan F, Stoklosa T, Iannaccone A, Negishi K, Marwick TH. Prognostic implications of LV strain risk score in asymptomatic patients with hypertensive heart disease. *JACC Cardiovasc Imaging*. 2016;9(8):911-21.
109. Pierdomenico SD, Lapenna D, Cuccurullo F. Regression of echocardiographic left ventricular hypertrophy after 2 years of therapy reduces cardiovascular risk in patients with essential hypertension. *Am J Hypertens*. 2008;21(4):464-70.
110. Wachtell K, Palmieri V, Olsen MH, Gerds E, Papademetriou V, Nieminen MS, et al. Change in systolic left ventricular performance after 3 years of antihypertensive treatment:the Losartan Intervention for Endpoint (LIFE) Study. *Circulation*. 2002;106(2):227-32.
111. Wachtell K, Bella JN, Rokkedal J, Palmieri V, Papademetriou V, Dahlöf B, et al. Change in diastolic left ventricular filling after one year of antihypertensive treatment:The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study. *Circulation*. 2002;105(9):1071-6.
112. Palmieri V, Bella JN, Arnett DK, Roman MJ, Oberman A, Kitzman DW, et al. Aortic root dilatation at sinuses of valsalva and aortic regurgitation in hypertensive and normotensive subjects:The Hypertension Genetic Epidemiology Network Study. *Hypertension*. 2001;37(5):1229-35.
113. Teixido-Tura G, Almeida AL, Choi EY, Gjesdal O, Jacobs DR Jr, Dietz HC, et al. Determinants of aortic root dilatation and reference values among young adults over a 20-year period:coronary artery risk development in young adults study. *Hypertension*. 2015;66(1):23-9.
114. Maron BJ, Epstein SE, Roberts WC. Causes of sudden death in competitive athletes. *J Am Coll Cardiol*. 1986;7(1):204-14.
115. Caselli S, Maron MS, Urbano-Moral JA, Pandian NG, Maron BJ, Pelliccia A. Differentiating left ventricular hypertrophy in athletes from that in patients with hypertrophic cardiomyopathy. *Am J Cardiol*. 2014;114(9):1383-9.
116. Caselli S, Montesanti D, Autore C, Di Paolo FM, Pisicchio C, Squeo MR, et al. Patterns of left ventricular longitudinal strain and strain rate in Olympic athletes. *J Am Soc Echocardiogr*. 2015;28(2):245-53.
117. Caselli S, Di Paolo FM, Pisicchio C, Pandian NG, Pelliccia A. Patterns of left ventricular diastolic function in Olympic athletes. *J Am Soc Echocardiogr*. 2015;28(2):236-44.
118. Maron BJ. Hypertrophic cardiomyopathy and other causes of sudden cardiac death in young competitive athletes, with considerations for preparticipation screening and criteria for disqualification. *Cardiol Clin*. 2007;25(3):399-414, vi.
119. Maron BJ, Thompson PD, Ackerman MJ, Balady G, Berger S, Cohen D, et al. Recommendations and considerations related to preparticipation screening for cardiovascular abnormalities in competitive athletes:2007 update:a scientific statement from the American Heart Association Council on Nutrition, Physical Activity, and Metabolism:endorsed by the American College of Cardiology Foundation. *Circulation*. 2007;115(12):1643-455.

120. Galderisi M, Cardim N, D'Andrea A, Bruder O, Cosyns B, Davin L, et al. The multi-modality cardiac imaging approach to the Athlete's heart: an expert consensus of the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16(4):353.
121. Etchells E, Bell C, Robb K. Does this patient have an abnormal systolic murmur? *JAMA*. 1997;277(7):564-71.
122. Chizner MA. Cardiac auscultation: rediscovering the lost art. *Curr Probl Cardiol*. 2008;33(7):326-408.
123. Cheitlin MD, Alpert JS, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, et al. ACC/AHA Guidelines for the Clinical Application of Echocardiography. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Clinical Application of Echocardiography). Developed in collaboration with the American Society of Echocardiography. *Circulation*. 1997;95(6):1686-744.
124. Shry EA, Smithers MA, Mascette AM. Auscultation versus echocardiography in a healthy population with precordial murmur. *Am J Cardiol*. 2001;87(12):1428-30.
125. Tavel ME. Cardiac auscultation. A glorious past—but does it have a future? *Circulation*. 1996;93(6):1250-3.
126. Siqueira VN, Mancuso FJ, Campos O, De Paola AA, Carvalho AC, Moises VA. Training program for cardiology residents to perform focused cardiac ultrasound examination with portable device. *Echocardiography*. 2015;32(10):1455-62.
127. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al. 2014 AHA/ACC guideline 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. *J Thorac Cardiovasc Surg*. 2014;148(1):e1-132.
128. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2017;70(2):252-89.
129. Harb SC, Griffin BP. Mitral valve disease: a comprehensive review. *Curr Cardiol Rep*. 2017;19(8):73.
130. Tsang W, Lang RM. Three-dimensional echocardiography is essential for intraoperative assessment of mitral regurgitation. *Circulation*. 2013;128(6):643-52;discussion 52.
131. Galli E, Lancellotti P, Sengupta PP, Donal E. LV mechanics in mitral and aortic valve diseases: value of functional assessment beyond ejection fraction. *JACC Cardiovasc Imaging*. 2014;7(11):1151-66.
132. Buck T, Plicht B. Real-Time three-dimensional echocardiographic assessment of severity of mitral regurgitation using proximal isovelocity surface area and vena contracta area method. Lessons we learned and clinical implications. *Curr Cardiovasc Imaging Rep*. 2015;8(10):38.
133. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2017;30(4):303-71.
134. Heo R, Son JW, B OH, Chang HJ, Kim YJ, Datta S, et al. Clinical implications of three-dimensional real-time color doppler transthoracic echocardiography in quantifying mitral regurgitation: a comparison with conventional two-dimensional methods. *J Am Soc Echocardiogr*. 2017;30(4):393-403 e7.
135. Casas-Rojo E, Fernandez-Golfín C, Moya-Mur JL, Gonzalez-Gomez A, Garcia-Martin A, Moran-Fernandez L, et al. Area strain from 3D speckle-tracking echocardiography as an independent predictor of early symptoms or ventricular dysfunction in asymptomatic severe mitral regurgitation with preserved ejection fraction. *Int J Cardiovasc Imaging*. 2016;32(8):1189-98.
136. Witkowski TG, Thomas JD, Debonnaire PJ, Delgado V, Hoke U, Ewe SH, et al. Global longitudinal strain predicts left ventricular dysfunction after mitral valve repair. *Eur Heart J Cardiovasc Imaging*. 2013;14(1):69-76.
137. Reyes VP, Raju BS, Wynne J, Stephenson LW, Raju R, Fromm BS, et al. Percutaneous balloon valvuloplasty compared with open surgical commissurotomy for mitral stenosis. *N Engl J Med*. 1994;331(15):961-7.
138. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al. 2014 AHA/ACC Guideline 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. *Circulation*. 2014;129(23):e521-643.
139. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Fleisher LA, et al. 2017 AHA/ACC Focused Update of the 2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. 2017;135(25):e1159-e95.
140. Evaluation of left ventricular structure and function. *Arq Bras Cardiol*. 2009;93(6 Suppl 3):e265-73.
141. Tarasoutchi F, Montera MW, Grinberg M, Pineiro DJ, Sanchez CR, Bacelar AC, et al. Brazilian Guidelines for Valve Disease - SBC 2011 / I Guideline Inter-American Valve Disease - 2011 SIAC. *Arq Bras Cardiol*. 2011;97(5 Suppl 1):1-67.
142. Karamnov S, Burbano-Vera N, Huang CC, Fox JA, Shernan SK. Echocardiographic assessment of mitral stenosis orifice area: a comparison of a novel three-dimensional method versus conventional techniques. *Anesth Analg*. 2017;125(3):774-80.
143. Esteves WAM, Lodi-Junqueira L, Soares JR, Sant'Anna Athayde GR, Goebel GA, Carvalho LA, et al. Impact of percutaneous mitral valvuloplasty on left ventricular function in patients with mitral stenosis assessed by 3D echocardiography. *Int J Cardiol*. 2017 Dec;248:280-5.
144. Lancellotti P, Pellikka PA, Budts W, Chaudhry FA, Donal E, Dulgheru R, et al. The Clinical Use of Stress Echocardiography in Non-Ischaemic Heart Disease: Recommendations from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2017;30(2):101-38.
145. Reis G, Motta MS, Barbosa MM, Esteves WA, Souza SF, Bocchi EA. Dobutamine stress echocardiography for noninvasive assessment and risk stratification of patients with rheumatic mitral stenosis. *J Am Coll Cardiol*. 2004;43(3):393-401.
146. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, et al. 2017 ESC/EACTS Guidelines for the management of valvular heart disease: The Task Force for the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2017;38(36):2739-91.
147. Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, et al. Recommendations on the Echocardiographic Assessment of Aortic Valve Stenosis: A Focused Update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2017;30(4):372-92.
148. Doherty JU, Kort S, Mehran R, Schoenhagen P, Soman P. ACC/AATS/AHA/AASE/ASNC/HRS/SCAI/SCCT/SCMR/STS 2017 Appropriate Use Criteria for Multimodality Imaging in Valvular Heart Disease: A Report of the American College of Cardiology Appropriate Use Criteria Task Force, American Association for Thoracic Surgery, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2017;70(13):1647-72.

Statement

149. Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP, 3rd, Guyton RA, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2014;63(22):2438-88.
150. Clavel MA, Burwash IG, Pibarot P. Cardiac Imaging for Assessing Low-Gradient Severe Aortic Stenosis. *JACC Cardiovasc Imaging*. 2017;10(2):185-202.
151. Rosenhek R, Binder T, Porenta G, Lang I, Christ G, Schemper M, et al. Predictors of outcome in severe, asymptomatic aortic stenosis. *N Engl J Med*. 2000;343(9):611-7.
152. Rosenhek R, Zilberszac R, Schemper M, Czerny M, Mundigler G, Graf S, et al. Natural history of very severe aortic stenosis. *Circulation*. 2010;121(1):151-6.
153. Stojnic BB, Brecker SJ, Xiao HB, Helmy SM, Mbaisouroum M and Gibson DG. Left ventricular filling characteristics in pulmonary hypertension: a new mode of ventricular interaction. *Br Heart J*. 1992;68(1):16-20.
154. Goldstein SA, Evangelista A, Abbara S, Arai A, Asch FM, Badano LP, et al. Multimodality imaging of diseases of the thoracic aorta in adults: from the American Society of Echocardiography and the European Association of Cardiovascular Imaging: endorsed by the Society of Cardiovascular Computed Tomography and Society for Cardiovascular Magnetic Resonance. *J Am Soc Echocardiogr*. 2015;28(2):119-82.
155. Iung B, Baron G, Butchart EG, Delahaye F, Gohlke-Barwolf C, Levang OW, et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. *Eur Heart J*. 2003;24(13):1231-43.
156. Unger P, Clavel MA, Lindman BR, Mathieu P, Pibarot P. Pathophysiology and management of multivalvular disease. *Nat Rev Cardiol*. 2016;13(7):429-40.
157. Unger P, Dedobbeleer C, Van Camp G, Plein D, Cosyns B, Lancellotti P. Mitral regurgitation in patients with aortic stenosis undergoing valve replacement. *Heart*. 2010;96(1):9-14.
158. Nombela-Franco L, Ribeiro HB, Urena M, Allende R, Amat-Santos I, DeLarochelliere R, et al. Significant mitral regurgitation left untreated at the time of aortic valve replacement: a comprehensive review of a frequent entity in the transcatheter aortic valve replacement era. *J Am Coll Cardiol*. 2014;63(24):2643-58.
159. Vahanian A, Alfieri O, Andreotti F, Antunes MJ, Baron-Esquivias G, Baumgartner H, et al. Guidelines on the management of valvular heart disease (version 2012): the Joint Task Force on the Management of Valvular Heart Disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur J Cardiothorac Surg*. 2012;42(4):S1-44.
160. Lang RM, Badano LP, Tsang W, Adams DH, Agricola E, Buck T, et al. EAE/ASE recommendations for image acquisition and display using three-dimensional echocardiography. *Eur Heart J Cardiovasc Imaging*. 2012;13(1):1-46.
161. Olmos C, Vilacosta I, Fernandez-Perez C, Bernal JL, Ferrera C, Garcia-Arribas D, et al. The evolving nature of infective endocarditis in Spain: a population-based study (2003 to 2014). *J Am Coll Cardiol*. 2017;70(22):2795-804.
162. Rahimtoola SH. The problem of valve prosthesis-patient mismatch. *Circulation*. 1978;58(1):20-4.
163. Yoganathan AP, Raghav V. fluid dynamics of prosthetic valves. In: Elsevier, (ed.). *Intraoperative and Interventional Echocardiography*. 2017.
164. Nunes MC, Gelape CL, Ferrari TC. Profile of infective endocarditis at a tertiary care center in Brazil during a seven-year period: prognostic factors and in-hospital outcome. *Int J Infect Dis*. 2010;14(5):e394-8.
165. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, et al. ACC/AHA/ASE 2003 Guideline Update for the Clinical Application of Echocardiography: summary article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASE Committee to Update the 1997 Guidelines for the Clinical Application of Echocardiography). *J Am Soc Echocardiogr*. 2003;16(10):1091-110.
166. Horstkotte D, Follath F, Gutschik E, Lengyel M, Oto A, Pavie A, et al. [Guidelines on prevention, diagnosis and treatment of infective endocarditis. Executive summary]. *Rev Esp Cardiol*. 2004;57(10):952-62.
167. Horstkotte D, Follath F, Gutschik E, Lengyel M, Oto A, Pavie A, et al. Guidelines on prevention, diagnosis and treatment of infective endocarditis executive summary; the task force on infective endocarditis of the European society of cardiology. *Eur Heart J*. 2004;25(3):267-76.
168. Bonow RO, Carabello BA, Chatterjee K, de Leon AC, Jr., Faxon DP, Freed MD, et al. 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 revise the 1998 guidelines for the management of patients with valvular heart disease). Endorsed by the Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2008;52(13):e1-142.
169. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F, et al. 2015 ESC Guidelines for the management of infective endocarditis: The Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). *Eur Heart J*. 2015;36(44):3075-128.
170. Galie N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J*. 2016;37(1):67-119.
171. Fisher MR, Forfia PR, Chamera E, Houston-Harris T, Champion HC, Girgis RE, et al. Accuracy of Doppler echocardiography in the hemodynamic assessment of pulmonary hypertension. *Am J Respir Crit Care Med*. 2009;179(7):615-21.
172. Bossone E, D'Andrea A, D'Alto M, Citro R, Argiento P, Ferrara F, et al. Echocardiography in pulmonary arterial hypertension: from diagnosis to prognosis. *J Am Soc Echocardiogr*. 2013;26(1):1-14.
173. Lee SE, An HY, Im JH, Sung JM, Cho JJ, Shim CY, et al. Screening of Mechanical Complications of Dilated Pulmonary Artery Related to the Risk for Sudden Cardiac Death in Patients with Pulmonary Arterial Hypertension by Transthoracic Echocardiography. *J Am Soc Echocardiogr*. 2016;29(6):561-6.
174. Konstantinides SV. 2014 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. *Eur Heart J*. 2014;35(45):3145-6.
175. Task Force M, Montalescot G, Sechtem U, Achenbach S, Andreotti F, Arden C, et al. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*. 2013;34(38):2949-3003.
176. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2016;37(3):267-315.
177. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Rev Esp Cardiol (Engl Ed)*. 2017;70(12):1082.

178. Douglas PS, Khandheria B, Stainback RF, Weissman NJ, Brindis RG, Patel MR, et al. ACCF/AHA/ACEP/ASNC/SCAI/SCCT/SCMR 2007 appropriateness criteria for transthoracic and transesophageal echocardiography: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American Society of Echocardiography, American College of Emergency Physicians, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society for Cardiovascular Magnetic Resonance endorsed by the American College of Chest Physicians and the Society of Critical Care Medicine. *J Am Coll Cardiol*. 2007;50(2):187-204.
179. Sicari R, Nihoyannopoulos P, Evangelista A, Kasprzak J, Lancellotti P, Poldermans D, et al. Stress Echocardiography Expert Consensus Statement-Executive Summary: European Association of Echocardiography (EAE) (a registered branch of the ESC). *Eur Heart J*. 2009;30(3):278-89.
180. Lancellotti P, Price S, Edvardsen T, Cosyns B, Neskovic AN, Dulgheru R, et al. The use of echocardiography in acute cardiovascular care: recommendations of the European Association of Cardiovascular Imaging and the Acute Cardiovascular Care Association. *Eur Heart J Acute Cardiovasc Care*. 2015;4(1):3-5.
181. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD, et al. Third universal definition of myocardial infarction. *Eur Heart J*. 2012;33(20):2551-67.
182. Zamorano J, Bax J, Knuuti J, Sechtem U, Lancellotti P, Badano L. The ESC textbook of cardiovascular imaging. second ed.: Oxford University Press, 2015.
183. Liou K, Negishi K, Ho S, Russell EA, Cranney G, Ooi SY. Detection of Obstructive Coronary Artery Disease Using Peak Systolic Global Longitudinal Strain Derived by Two-Dimensional Speckle-Tracking: A Systematic Review and Meta-Analysis. *J Am Soc Echocardiogr*. 2016;29(8):724-35 e4.
184. American College of Cardiology Foundation Appropriate Use Criteria Task F, American Society of E, American Heart A, American Society of Nuclear C, Heart Failure Society of A, Heart Rhythm S, et al. ACCF/AHA/ASNC/HFSA/HRS/SCAI/SCCM/SCCT/SCMR 2011 Appropriate Use Criteria for Echocardiography. A Report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Society of Echocardiography, American Heart Association, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Critical Care Medicine, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance American College of Chest Physicians. *J Am Soc Echocardiogr*. 2011;24(3):229-67.
185. Porter TR, Abdelmoneim S, Belcik JT, McCulloch ML, Mulvagh SL, Olson JJ, et al. Guidelines for the cardiac sonographer in the performance of contrast echocardiography: a focused update from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2014;27(8):797-810.
186. Wolk MJ, Bailey SR, Doherty JU, Douglas PS, Hendel RC, Kramer CM, et al. ACCF/AHA/ASE/ASNC/HFSA/HRS/SCAI/SCCT/SCMR/STS 2013 multimodality appropriate use criteria for the detection and risk assessment of stable ischemic heart disease: a report of the American College of Cardiology Foundation Appropriate Use Criteria Task Force, American Heart Association, American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Failure Society of America, Heart Rhythm Society, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, Society for Cardiovascular Magnetic Resonance, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. 2014;63(4):380-406.
187. Romano MMD, Branco M, Turin Moreira H, Schmidt A, Kisslo J, Maciel BC. Appropriate use of echocardiography and relation to clinical decision making in both inpatients and outpatients in a developing country. *Echocardiography*. 2018;35(1):9-16.
188. Cesar LA, Ferreira JF, Armaganijan D, Gowdak LH, Mansur AP, Bodanese LC, et al. Guideline for stable coronary artery disease. *Arq Bras Cardiol*. 2014;103(2 Suppl 2):1-56.
189. Sicari R. Perioperative risk stratification in non cardiac surgery: role of pharmacological stress echocardiography. *Cardiovasc Ultrasound*. 2004 May;2:4.
190. Lonnebakken MT, Bleie O, Strand E, Staal EM, Nygard OK, Gerds E. Myocardial contrast echocardiography in assessment of stable coronary artery disease at intermediate dobutamine-induced stress level. *Echocardiography*. 2009;26(1):52-60.
191. Mulvagh SL, Rakowski H, Vannan MA, Abdelmoneim SS, Becher H, Bierig SM, et al. American Society of Echocardiography Consensus Statement on the Clinical Applications of Ultrasonic Contrast Agents in Echocardiography. *J Am Soc Echocardiogr*. 2008;21(11):1179-201;quiz 281.
192. Gibson PH, Becher H, Choy JB. The current state of myocardial contrast echocardiography: what can we read between the lines? *Eur Heart J Cardiovasc Imaging*. 2014;15(3):351.
193. Gaibazzi N, Reverberi C, Lorenzoni V, Molinaro S, Porter TR. Prognostic value of high-dose dipyridamole stress myocardial contrast perfusion echocardiography. *Circulation*. 2012;126(10):1217-24.
194. Gaibazzi N, Silva L, Reverberi C. Safety and positive predictive value of high-dose dipyridamole stress-echocardiography with or without contrast flash-replenishment perfusion imaging in patients with suspected or known coronary artery disease. *Int J Cardiol*. 2012;154(3):382-3.
195. Senior R, Moreo A, Gaibazzi N, Agati L, Tiemann K, Shivalkar B, et al. Comparison of sulfur hexafluoride microbubble (SonoVue)-enhanced myocardial contrast echocardiography with gated single-photon emission computed tomography for detection of significant coronary artery disease: a large European multicenter study. *J Am Coll Cardiol*. 2013;62(15):1353-61.
196. Fukuda S, Hozumi T, Muro T, Watanabe H, Hyodo E, Yoshiyama M, et al. Quantitative intravenous myocardial contrast echocardiography predicts recovery of left ventricular function after revascularization in chronic coronary artery disease. *Echocardiography*. 2004;21(2):119-24.
197. Grysiewicz RA, Thomas K, Pandey DK. Epidemiology of ischemic and hemorrhagic stroke: incidence, prevalence, mortality, and risk factors. *Neurol Clin*. 2008;26(4):871-95, vii.
198. Mansur AP, do Souza MF, Favarato D, Avakian SD, César LA, Aldrigui JM, et al. Stroke and ischemic heart disease mortality trends in Brazil from 1979 to 1996. *Neuroepidemiology*. 2003;22(3):179-83.
199. Garritano CR, Luz PM, Pires ML, Barbosa MT, Batista KM. Analysis of the mortality trend due to cerebrovascular accident in Brazil in the XXI century. *Arq Bras Cardiol*. 2012;98(6):519-27.
200. Lavados PM, Hennis AJ, Fernandes JG, Medina MT, Legetic B, Hoppe A, et al. Stroke epidemiology, prevention, and management strategies at a regional level: Latin America and the Caribbean. *Lancet Neurol*. 2007;6(4):362-72.
201. Strandberg M, Marttila RJ, Helenius H, Hartiala J. Transoesophageal echocardiography in selecting patients for anticoagulation after ischaemic stroke or transient ischaemic attack. *J Neurol Neurosurg Psychiatry*. 2002;73(1):29-33.
202. Petty GW, Brown RD, Jr., Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of incidence and risk factors. *Stroke*. 1999;30(12):2513-6.
203. Kolominsky-Rabas PL, Weber M, Gefeller O, Neundorfer B, Heuschmann PU. Epidemiology of ischemic stroke subtypes according to TOAST criteria: incidence, recurrence, and long-term survival in ischemic stroke subtypes: a population-based study. *Stroke*. 2001;32(12):2735-40.
204. Kim JT, Yoo SH, Kwon JH, Kwon SU, Kim JS. Subtyping of ischemic stroke based on vascular imaging: analysis of 1,167 acute, consecutive patients. *J Clin Neurol*. 2006;2(4):225-30.
205. Adams Jr HP, Bendixen BH. Low- versus high-dose aspirin in prevention of ischemic stroke. *Clin Neuropharmacol*. 1993;16(6):485-500.

Statement

206. Witt BJ, Brown Jr RD, Jacobsen SJ, Weston SA, Ballman KV, Meverden RA, et al. Ischemic stroke after heart failure: a community-based study. *Am Heart J*. 2006;152(1):102-9.
207. Wang Y, Lichtman JH, Dharmarajan K, Masoudi FA, Ross JS, Dodson JA, et al. National trends in stroke after acute myocardial infarction among Medicare patients in the United States: 1999 to 2010. *Am Heart J*. 2015;169(1):78-85 e4.
208. Cannegieter SC, Rosendaal FR, Briet E. Thromboembolic and bleeding complications in patients with mechanical heart valve prostheses. *Circulation*. 1994;89(2):635-41.
209. Garcia-Cabrera E, Fernandez-Hidalgo N, Almirante B, Ivanova-Georgieva R, Noureddine M, Plata A, et al. Neurological complications of infective endocarditis: risk factors, outcome, and impact of cardiac surgery: a multicenter observational study. *Circulation*. 2013;127(23):2272-84.
210. Amarenco P, Cohen A, Hommel M, Moulin T, Leys D, et al; French Study of Aortic Plaques in Stroke Group. Atherosclerotic disease of the aortic arch as a risk factor for recurrent ischemic stroke. *N Engl J Med*. 1996;334(19):1216-21.
211. Handke M, Harloff A, Olschewski M, Hetzel A, Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. *N Engl J Med*. 2007;357(22):2262-8.
212. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP; Investigators PFOiCSS. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation*. 2002;105(22):2625-31.
213. Ferro JM. Cardioembolic stroke: an update. *Lancet Neurol*. 2003;2(3):177-88.
214. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland Jr JC, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines and the Heart Rhythm Society. *Circulation*. 2014;130(23):2071-104.
215. Chugh SS, Roth GA, Gillum RF, Mensah GA. Global burden of atrial fibrillation in developed and developing nations. *Glob Heart*. 2014;9(1):113-9.
216. Colilla S, Crow A, Petkun W, Singer DE, Simon T, Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the U.S. adult population. *Am J Cardiol*. 2013;112(8):1142-7.
217. Zoni-Berisso M, Lercari F, Carazza T, Domenicucci S. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol*. 2014 Jun;6:213-20.
218. Lloyd-Jones DM, Wang TJ, Leip EP, Larson MG, Levy D, Vasan RS, et al. Lifetime risk for development of atrial fibrillation: the Framingham Heart Study. *Circulation*. 2004;110(9):1042-6.
219. Magalhães LP, Figueiredo MJO, Cintra FD, Saad EB, Kuniyoshi RR, Menezes Lorga Filho A, et al. Executive Summary of the II Brazilian Guidelines for Atrial Fibrillation. *Arq Bras Cardiol*. 2016;107(6):501-8.
220. Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. *Eur Heart J*. 2016;37(38):2893-962.
221. Donal E, Lip GY, Galderisi M, Goette A, Shah D, Marwan M, et al. EACVI/EHRA Expert Consensus Document on the role of multi-modality imaging for the evaluation of patients with atrial fibrillation. *Eur Heart J Cardiovasc Imaging*. 2016;17(4):355-83.
222. Donal E, Colette E, Hubert A. Could transthoracic echocardiography results be convincing enough to impact the management of atrial fibrillation? *Echocardiography*. 2016;33(5):672-3.
223. Maybrook RJ, Afzal MR, Parashar S, Deibert B, Chivington M, Walker JY, et al. Intrinsic and extrinsic cardiac pseudotumors: echocardiographic evaluation and review of the literature. *Echocardiography*. 2016;33(1):117-32.
224. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances Since the 2004 Classification. *J Thorac Oncol*. 2015;10(9):1243-60.
225. Butany J, Leong SW, Carmichael K, Komeda M. A 30-year analysis of cardiac neoplasms at autopsy. *Can J Cardiol*. 2005;21(8):675-80.
226. Maleszewski JJ, Anavekar NS, Moynihan TJ, Klarich KW. Pathology, imaging, and treatment of cardiac tumours. *Nat Rev Cardiol*. 2017;14(9):536-49.
227. Mankad R, Herrmann J. Cardiac tumors: echo assessment. *Echo Res Pract*. 2016;3(4):R65-77.
228. Zaragoza-Macias E, Chen MA, Gill EA. Real time three-dimensional echocardiography evaluation of intracardiac masses. *Echocardiography*. 2012;29(2):207-19.
229. Dujardin KS, Click RL, Oh JK. The role of intraoperative transesophageal echocardiography in patients undergoing cardiac mass removal. *J Am Soc Echocardiogr*. 2000;13(12):1080-3.
230. Lepper W, Shivalkar B, Rinkevich D, Belcik T, Wei K. Assessment of the vascularity of a left ventricular mass using myocardial contrast echocardiography. *J Am Soc Echocardiogr*. 2002;15(11):1419-22.
231. Douglas PS, Khandheria B, Stainback RF, Weissman NJ, Brindis RG, Patel MR, et al. ACCF/AHA/ACEP/ASNC/SCAI/SCCT/SCMR 2007 appropriateness criteria for transthoracic and transesophageal echocardiography: a report of the American College of Cardiology Foundation Quality Strategic Directions Committee Appropriateness Criteria Working Group, American Society of Echocardiography, American College of Emergency Physicians, American Society of Nuclear Cardiology, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and the Society for Cardiovascular Magnetic Resonance endorsed by the American College of Chest Physicians and the Society of Critical Care Medicine. *J Am Coll Cardiol*. 2007;50(2):187-204.
232. Steeds RP, Garbi M, Cardim N, Kasprzak JD, Sade E, Nihoyannopoulos P, et al. EACVI appropriateness criteria for the use of transthoracic echocardiography in adults: a report of literature and current practice review. *Eur Heart J Cardiovasc Imaging*. 2017;18(11):1191-204.
233. Adler Y, Charron P. The 2015 ESC Guidelines on the diagnosis and management of pericardial diseases. *Eur Heart J*. 2015;36(42):2873-4.
234. Silvestry FE, Kerber RE, Brook MM, Carroll JD, Eberman KM, Goldstein SA, et al. Echocardiography-guided interventions. *J Am Soc Echocardiogr*. 2009;22(3):213-31; quiz 316-7.
235. Barberato SH. Ecocardiografia em condições clínicas especiais: doenças sistêmicas, no idoso, na gestante e no atleta. In: Moreira MCV, Montenegro ST, Paola AAV, (eds.). Livro-texto da Sociedade Brasileira de Cardiologia. 2a ed. São Paulo: Manole; 2015. p.1699-1703
236. Pecoits-Filho R, Barberato SH. Echocardiography in chronic kidney disease: diagnostic and prognostic implications. *Nephron Clin Pract*. 2010;114(4):c242-7.
237. Pecoits-Filho R, Bucharles S, Barberato SH. Diastolic heart failure in dialysis patients: mechanisms, diagnostic approach, and treatment. *Semin Dial*. 2012;25(1):35-41.
238. Barberato SH, Bucharles SG, Sousa AM, Costantini CO, Costantini CR, Pecoits-Filho R. Prevalence and prognostic impact of diastolic dysfunction in patients with chronic kidney disease on hemodialysis. *Arq Bras Cardiol*. 2010;94(4):457-62.
239. K/DOQI Workgroup. K/DOQI clinical practice guidelines for cardiovascular disease in dialysis patients. *Am J Kidney Dis*. 2005;45(4 Suppl 3):S1-153.
240. Habib G, Bucciarelli-Ducci C, Caforio ALP, Cardim N, Charron P, Cosyns B, et al. Multimodality Imaging in Restrictive Cardiomyopathies: An EACVI expert consensus document In collaboration with the "Working Group on myocardial and pericardial diseases" of the European Society

- of Cardiology Endorsed by The Indian Academy of Echocardiography. *Eur Heart J Cardiovasc Imaging*. 2017;18(10):1090-121.
241. Writing group; Document reading group; EACVI Reviewers: This document was reviewed by members of the EACVI Scientific Documents Committee for 2014–2016 and 2016–2018. A joint procedural position statement on imaging in cardiac sarcoidosis: from the Cardiovascular and Inflammation & Infection Committees of the European Association of Nuclear Medicine, the European Association of Cardiovascular Imaging, and the American Society of Nuclear Cardiology. *Eur Heart J Cardiovasc Imaging*. 2017;18(10):1073-89.
 242. Barberato SH, Barbosa-Ferreira JM, Fernandes F. Tumores cardíacos. In: Moreira MCV, Montenegro ST, Paola AA, (eds.). *Livro texto da Sociedade Brasileira de Cardiologia*. Manole, Barueri-SP, 2015, p. 1152-56.
 243. Lin FY, Devereux RB, Roman MJ, Meng J, Jow VM, Jacobs A, et al. Assessment of the thoracic aorta by multidetector computed tomography: age- and sex-specific reference values in adults without evident cardiovascular disease. *J Cardiovasc Comput Tomogr*. 2008;2(5):298-308.
 244. Zehr KJ, Orszulak TA, Mullany CJ, Matloobi A, Daly RC, Dearani JA, et al. Surgery for aneurysms of the aortic root: a 30-year experience. *Circulation*. 2004;110(11):1364-71.
 245. Erbel R, Aboyans V, Boileau C, Bossone E, Di Bartolomeo R, Eggebrecht H, et al. 2014 ESC Guidelines on the diagnosis and treatment of aortic diseases. *Kardiol Pol*. 2014;72(12):1169-252.
 246. Irwin RB, Greaves M, Schmitt M. Left superior vena cava: revisited. *Eur Heart J Cardiovasc Imaging*. 2012;13(4):284-91.
 247. American Society of A and Society of Cardiovascular Anesthesiologists Task Force on Transesophageal E. Practice guidelines for perioperative transesophageal echocardiography. An updated report by the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists Task Force on Transesophageal Echocardiography. *Anesthesiology*. 2010;112(5):1084-96.
 248. Schulmeyer MC, Iglesias I, Falconi M, Spina S. Primeras recomendaciones clínicas latinoamericanas para ecocardiografía perioperatoria. ECOSIAC (Asociación de Ecocardiografía e Imágen Cardiovascular de la Sociedad Interamericana de Cardiología). Grupo de trabajo en Ecocardiografía Perioperatoria. *Rev Chil Anest*. 2017;46(3):145-56.
 249. Porter TR, Shillcutt SK, Adams MS, Desjardins G, Glas KE, Olson JJ, et al. Guidelines for the use of echocardiography as a monitor for therapeutic intervention in adults: a report from the American Society of Echocardiography. *J Am Soc Echocardiogr*. 2015;28(1):40-56.
 250. Salgado-Filho MF, Morhy SS, Vasconcelos HD, Lineburger EB, Papa FV, Botelho ES, et al. Consensus on perioperative transesophageal echocardiography of the Brazilian Society of Anesthesiology and the department of cardiovascular image of the Brazilian Society of Cardiology. *Rev Bras Anesthesiol*. 2018;68(1):1-32.
 251. Bartakian S, El-Said HG, Printz B, Moore JW. Prospective randomized trial of transthoracic echocardiography versus transesophageal echocardiography for assessment and guidance of transcatheter closure of atrial septal defects in children using the Amplatzer septal occluder. *JACC Cardiovasc Interv*. 2013;6(9):974-80.
 252. Nunes MC, Tan TC, Elmariah S, do Lago R, Margey R, Cruz-Gonzalez I, et al. The echo score revisited: Impact of incorporating commissural morphology and leaflet displacement to the prediction of outcome for patients undergoing percutaneous mitral valvuloplasty. *Circulation*. 2014;129(8):886-95.
 253. Wilkins GT, Weyman AE, Abascal VM, Block PC, Palacios IF. Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. *Br Heart J*. 1988;60(4):299-308.
 254. Tamborini G, Fusini L, Gripari P, Muratori M, Cefalu C, Maffessanti F, et al. Feasibility and accuracy of 3DTEE versus CT for the evaluation of aortic valve annulus to left main ostium distance before transcatheter aortic valve implantation. *JACC Cardiovasc Imaging*. 2012;5(6):579-88.

Statement



Este é um artigo de acesso aberto distribuído sob os termos da licença de atribuição pelo Creative Commons

May issue of 2019, vol. 112 (5), pages 577-587

In review article “Kidney Disease in Diabetes Mellitus: Cross-Linking between Hyperglycemia, Redox Imbalance and Inflammation”, consider Sandra Mary Lima Vasconcelos as the correct form for the name of the author Sandra Mary de Lima Vasconcelos.

May issue of 2019, vol. 112 (6), pages 713-714

In special article “ Heart Failure Awareness Day: A Tribute to the Genius Carlos Chagas”, consider Maria Christiane Valéria Braga Braile as the correct form for the name of the author Maria Cristiane Valeria Braga Braile.